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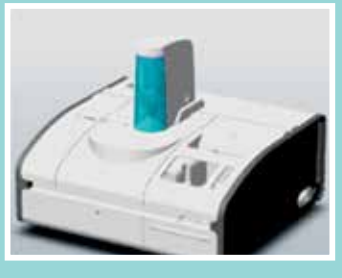

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Autopsy Reports of COVID-19 Patients

- Every organ in the body seems to be affected.
- Conducting autopsies on coronavirus disease (COVID) patients has been like a police line-up where it might not be possible to identify the perpetrator but it may be possible to eliminate the unlikely suspects.
- Autopsy has revealed that there's no direct tissue pathology that can explain the acute symptoms seen in the heart, kidney and brain.
- Certain hypotheses have been postulated regarding the causes of extensive organ damage in COVID-19. One of them states that hypoxia resulting from compromised lung function may cause secondary injuries.
- Obesity is a predisposing factor in the infected for worse morbidity and mortality. Obesity in itself is a pathologic state. It causes atherosclerosis, increased clotting, fatty liver disease and often, enlarged hearts.
- Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has shown a selectivity for the lungs. In one of the deceased, bone marrow response was observed with many myeloid precursors in the peripheral blood vessels, which is characteristic of an overwhelming infection.
- SARS-CoV-2 may be targeting the type II pneumocytes.
- These lung surface cells secrete a fatty substance that keeps the lobes pliable. And that is accountable for the diffuse alveolar damage and acute respiratory failure.
- Immunohistochemistry testing and electron microscopy have confirmed viral tropism for pulmonary II pneumocytes.
- Viral antigen in lung tissue has been found to be higher than with SARS or MERS (Middle East respiratory syndrome).
- Extensive detection in epithelial cells of the upper respiratory tract is unique among these highly pathogenic coronaviruses.
- Autopsies have also confirmed the reports of increased clotting. The virus may be infiltrating the endothelium and causing injury to the blood vessel.
- Myocarditis is typical of viral diseases, but it has been inconsistent in COVID-19 autopsies. Most have reported very little inflammation of the heart muscle. At least one death has been directly related to COVID-19-induced lymphohistiocytic and eosinophilic myocarditis. Researchers from Germany have reported in *JAMA Cardiology* that 60 out of 100 patients who had recovered from COVID-19 had ongoing myocardial inflammation, as evidenced by cardiovascular magnetic resonance imaging (MRI).

- But, it looks like, what they see on MRI is not true myocarditis but something else as per Richard S. Vander Heide, MD, PhD, MBA, a professor of pathology at Louisiana State University Health Sciences Center in New Orleans.
- Thus far, autopsy studies have shown no typical myocarditis in nearly every case.
- Vander Heide and colleagues reported cardiopulmonary findings from 10 autopsies on African Americans who died from COVID-19 in *The Lancet* in May. The report was updated with additional 12 cases in *Circulation* in July. Six of these 22 were found to have a history of heart disease. All had diffuse alveolar damage, which is a histopathologic marker of acute respiratory distress syndrome (ARDS), in addition to pulmonary thrombi and microangiopathy. The virus was not found in the heart muscle cells and there was no evidence of typical lymphocytic myocarditis. In the newer study, investigators used electron microscopy to find what appeared to be viral particles in the vascular cells in the heart, lungs and kidneys. Vander Heide, whose primary research interest is myocardial cell injury and adaptation, believes that the infection of these endothelial cells is resulting in clotting abnormalities in the heart's small vessels, causing inflammation. The heart cells are dying, but that can't be attributed to myocarditis. According to him, it's likely that the clotting is causing cell death from ischemia.
- Some pathologists are evaluating the vascular changes, which are among the unique features of COVID-19, according to Maximilian Ackermann, MD, and colleagues in an article published in May in the *New England Journal of Medicine*.
- Comparing the lungs of 7 patients who died from COVID-19 with 7 who died from acute respiratory distress syndrome (ARDS) secondary to influenza, and those from 10 age-matched, uninfected patients, investigators noted that the COVID-19 lungs exhibited severe endothelial injury, which appeared to be associated with intracellular SARS-CoV-2 virus.
- There was extensive vascular thrombosis with microangiopathy and occlusion of alveolar capillaries and significant new vessel growth from an unusual form of angiogenesis, known as intussusceptive angiogenesis — a reactive formation of new vessels where one splits into two.
- Investigators have also observed venous thromboembolism in patients, including in a study at the University Medical Center Hamburg-Eppendorf in Germany that was published in May in the *Annals of Internal Medicine*.
- Coronavirus infections may trigger venous thromboembolism.
- The potential mechanisms include endothelial dysfunction, systemic inflammation, and a procoagulatory state.
- Investigators at Hospital Graz II in Graz, Austria, also focused on thrombosis, with evidence of it in all 11 autopsies, reported an article published in *Annals of Internal Medicine*.
- While pathologists were initially not willing to conduct COVID-19 autopsies, particularly those that would involve aerosol-generating procedures, the College of American Pathologists worked towards lessening the fears and came out with guidelines that recommend techniques that minimize those procedures, including using hand shears or other alternatives to an oscillating bone saw (also recommended by the CDC) or using a vacuum shroud with the bone saw.
- There have been no reported cases of SARS-CoV-2 transmission from a corpse to any pathologist, morgue technician or assistant. An informal survey in March of pathologists on a LISTSERV revealed that only 6 out of 50 respondents were conducting autopsies. A month later, that number rose to 30.
- The CDC recommends that autopsies should be done in a negative pressure suite, which are more common at academic centers.

With input from Dr Monica Vasudev (Medscape excerpts)

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Flow Cytometer: The Need of Modern Hematology Laboratory

HARSHITA DUBEY*, AMAR RANJAN†, MANSI MODI‡, RIMLEE DUTTA#, LAWANYA RANJAN¥, SMRITI KHATRI£

ABSTRACT

Indeed, laboratory diagnosis is rapidly changing from what it was in the past to the present. Nowadays, flow cytometer (FCM) has become a novel introduction to the modern diagnostic technique, mainly in the field of hematology. In case of acute leukemia, peripheral blood, bone marrow examination, cytochemistry and immunohistochemistry for differentiation of myeloid or lymphoid lineage is required, which is feasible by flow cytometry. It has dramatically improved the diagnostic efficiency and reduced the duration of sampling along with better diagnostic outcomes as well as provided efficient therapeutic monitoring of any drug or drug regimen. It has also opened some more sensitive therapeutic plans, like monitoring "Minimal residual disease (MRD)", which is not possible without FCM. Detection of MRD has led to improved overall survival of patients. It has also opened up huge opportunities for research, which has become an important part of academic curriculum nowadays. Considering the importance and absolute necessity for better outcomes in hematology, the knowledge of basic principle of FCM becomes indispensable. Here, we try to elucidate the elementary components of this technique and also highlight its uses.

Keywords: Flow cytometer, hematology, immunohistochemistry

Flow cytometer (FCM) is a powerful technique for diagnosing multiple characteristics of a single cell. This technique is based on both qualitative and quantitative estimation. In the present era, FCM has made the transition from a research tool to a prerequisite in a laboratory dealing with hematolymphoid malignancy. It is useful not only in diagnosis for initiation of therapy, but also in therapeutic monitoring during follow-up. With the advent of prognostically useful antibodies, use of multicolor flow cytometry has become of utmost importance in the diagnosis and management of hematolymphoid diseases. Looking at the importance of this equipment, we need to have an elementary knowledge of its principle.

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Literally, the word 'flow' means to pass, 'cyto' means cell and 'metry' means measurement. Thus, flow cytometry translates to the passage of cells in a single file (line or row) in front of a laser beam to be detected, counted and sorted. The cells are labeled with fluorochromes and when excited by laser beams of appropriate wavelength, they emit light (fluorescence), which is filtered and collected. Specialized software converts the result into a digitalized (numerical) value.

Integral Components of FCM: The key components are being described below:

Fluidics: Cells of interest flow through a liquid stream called the sheath fluid. The speed of cells is higher than the speed of sheath fluid. This results in streamlining of cells in a single line (linear file). This mechanism is called hydrodynamic focusing. Up to 50,000 cells/sec can be measured, but the normal throughput is 1,000-10,000 cells/sec.

Interrogation point: Inside a FCM, cells in suspension are drawn into a stream created by a surrounding sheath of isotonic fluid. This creates a laminar flow which enables the cells to pass individually through an interrogation point. At this point, fluorochrome tagged cells pass through a laser beam causing its light (and that of the fluorochromes present) to scatter in all directions. These are collected through optics that direct

the light to a series of filters and mirrors, which isolate particular wavelength bands.

Scattering of light: Physical characteristics of a cell, such as size and internal complexity, like granularity, can help identify different cell populations like blasts, plasma cells, monocytes, etc. This diversity in different cell populations is identified using two parameters - forward and side scatter. Forward scatter (FSC) is based on two properties: size and refractive index. The FSC intensity is based on the particle's size and can also be used to distinguish between cellular debris and living cells. Side scatter (SSC) is based on the granularity or internal complexity. The more granular the cell, the more side scatter light is generated. Dead cells have lower FSC and higher SSC than living cells. The detector placed in the line of light beam measures forward scattering (FSC) [size] and that placed perpendicular to the light stream measures side scattering (SSC) [granularity, nuclear structure].

Electronics: The light signals are detected by photomultiplier (PMT) tubes and undergo digitization for computer analysis. Figure 1 depicts a schematic diagram of the components of a FCM.

For all practical purposes, cells falling in the range of 3-20 μ diameter can be analyzed using this technique. Identification of cells at a frequency of as low as 0.0001% has been reported to be possible by flow cytometry. Fluorescent dyes may bind with different cellular components like DNA or RNA. Antibodies conjugated to fluorescent dye have the potential to bind specific proteins on cell membranes or inside the cells. When a fluorochrome labeled cell is passed through a light source, the fluorescent molecules get excited and achieve a higher energy state. As they return to their resting states, the fluorochromes emit light energy at different wavelengths.

Several properties of a cell can be measured simultaneously by using multiple fluorochromes. Each fluorochrome with similar excitation wavelengths and different emission wavelengths (or colors) enables the measurement of several cell properties. Most commonly used dyes are propidium iodide, phycoerythrin, fluorescein, etc. Tandem dyes with internal fluorescence resonance energy transfer can create even longer wavelengths and more colors.

Information about physical and chemical structure of cells gathered is used in diagnosis of diseases. Samples used are bone marrow aspirates, blood, body fluid and tissue. For tissue samples, dissociation to single cells is required. Equipment for tissue dissociation is available commercially.

Getting numerical values: Photons collected by detectors get converted into electrical energy (current) to give a digitized value through "Analog to Digital Converter". Common softwares used are Caluja, CellQuest, Flowjo, FCS Express (FCS: Fluorescence-activated cell sorting), etc.

Gating: This refers to the isolation of subsets of cells on a plot. Gates can be visualized as barriers placed around cell populations having common characteristics

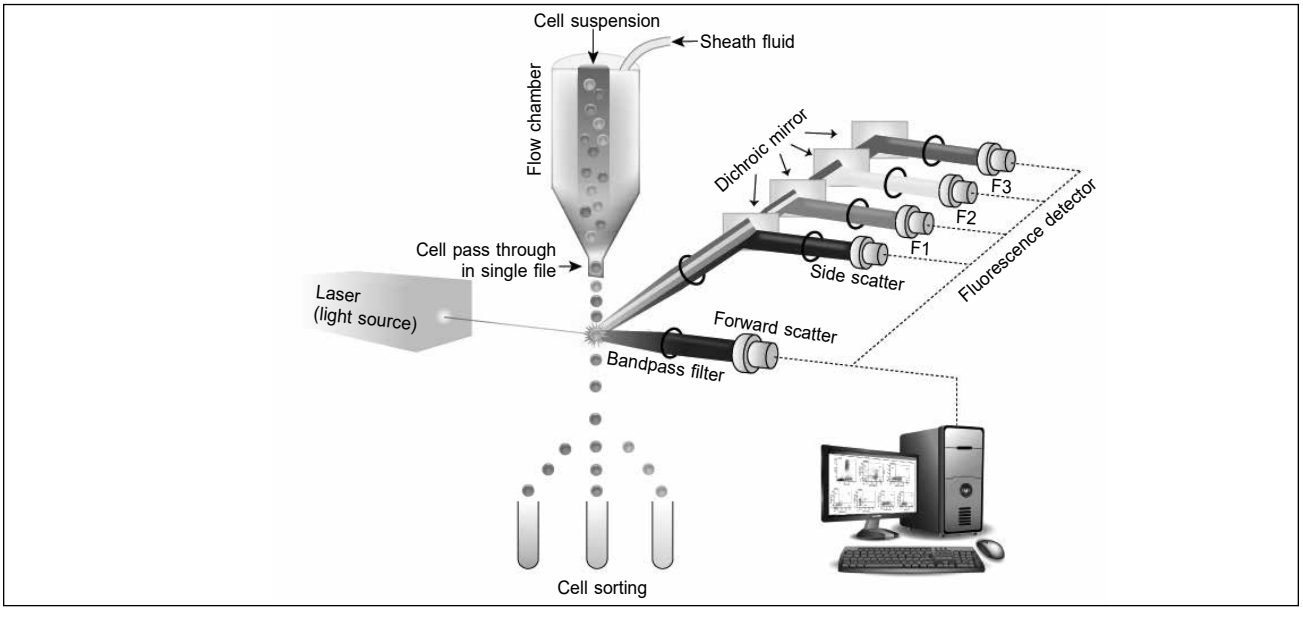

Figure 1. Schematic diagram of a flow cytometer.

like scatter or cluster of differentiation (CD) marker expression to isolate, quantify and study these subpopulations. Initially, cells are gated on the basis of FSC and SSC properties. After initial isolation and quantification of the population of interest, further division into subpopulations based on surface (or intracellular) markers is done. Back gating is a method for elimination of nonspecific staining and false positives. Here, the population identified by a particular gate is gated again on entirely different parameters for confirmation.

In Figure 2, we can understand the different cell clusters produced after running in FCM. Each cluster is gated using specialized software (caluja) and it is analyzed for any abnormality. Cluster of blasts can be identified in the image and its percentage can be used for analyzing presence or absence of malignancy.

COMPARISON OF FLOW CYTOMETRY WITH IMMUNOHISTOCHEMISTRY

Immunohistochemistry, in the past decade, has been popularly called as the brown revolution, due to its surmount importance in diagnosis.

However, the emergence of flow cytometry has made it possible to overcome the shortcomings of immunohistochemistry (IHC). It is a time-consuming technique restricted by the use of limited number of CD markers on a particular tissue section. The quantification of cells and enumeration of the different cell subtypes are also not possible via this technique. On the other hand, using flow cytometry, multicolor immunophenotyping is possible whereby large number of CD markers can be used simultaneously. This makes it possible to analyze numerous cells at the same time. Numerous parameters can be examined at once. Sometimes, the presence of two co-existent pathologies may be detected. Dead cells may also be gated using the analysis.

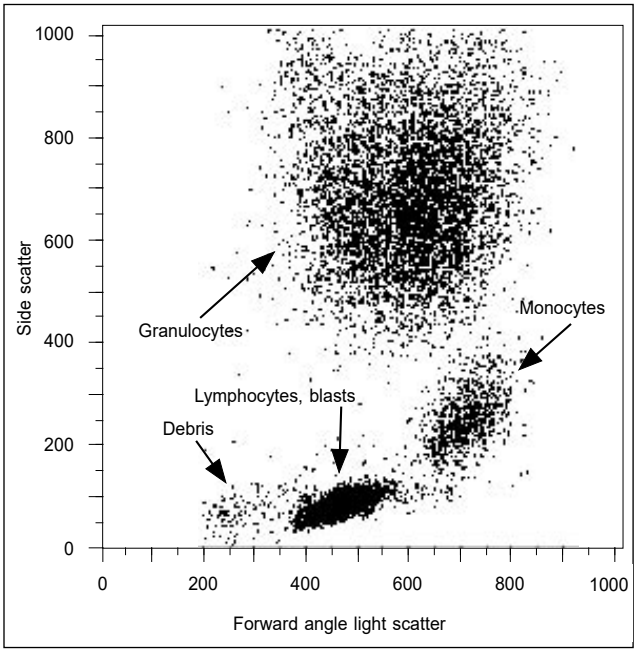

Figure 2. Dot plot of forward light scatter and side scatter.

Image source: Riley RS, Idowu M. Principles and applications of flow cytometry. Available at: http://www.flowlab-childrens-harvard.com/yahoo_site_admin/assets/docs/PRINCIPLESANDAPPLICATION.29464931.pdf

There is no need of a tissue biopsy. Even small quantities of samples such as body fluids, peripheral blood or fine needle aspirate specimens can be processed and identification of cells at a frequency as low as 0.001% is possible. Studies show that it is a rapid process requiring less effort. The only drawback of FCM as compared to IHC is that unlike in IHC, the localization of antigen (nuclear, cytoplasmic or membranous) is not possible in FCM.

USES OF FLOW CYTOMETRY

Flow cytometer is used to detect the size of cells and also to incorporate various hematological parameters, like to enumerate red blood cell (RBC), platelets size and white blood cell (WBC) based on light scatter. Moreover, bone marrow aspirate, cerebrospinal fluid and peripheral blood are all specimens that can be analyzed using flow cytometry (only viable cells can be analyzed). If the sample does not carry viable cells, flow cytometry analysis does not seem to be an option. FCM is also used in predicting leukemic cell lineages in peripheral blood of dogs and cats.

Measurement of DNA content was one of the earliest uses of flow cytometry. A 67% increase in DNA content was noted in malignant cells compared to nonmalignant cells. Tumor cells that are not diploid have an abnormal number of chromosomes that lead to an aneuploidy cell. Moreover, flow cytometric analysis of nuclear DNA content will demonstrate histogram peaks for nuclei of the sample that is in different phases of the cell cycle - $G0/G_1$, S-phase and G_2/M. Thus, it is used to determine the DNA content and ploidy of tumors. Retrospective studies examined the relationship between DNA abnormalities and duration of survival in patients with oncologic disease in an attempt to predict prognosis.

Phenotyping, the identification of particular observable characteristics, is one of the uses of flow cytometry in oncology. There are many phenotypic designations to differentiate healthy cells from tumor cells. Table 1 provides basic CD specification for common immune

Table 1. The Basic CD and Immune Cells Designation

Immune cell type	CD designation
B-cell	CD19, CD20, CD22
T-cell	CD1, CD3, CD4, CD5, CD7, CD8
Myeloid cells	CD13, CD33, CD117
Blasts	CD34, CD38, HLA DR
Monocyte	CD14, CD64
Macrophage	CD68, CD14, CD64, CD11b
Granulocytes	CD13, CD15, CD16, MPO
Megakaryocytes	CD41, CD42, CD62
RBC	CD36, CD235a

cell phenotypes. In addition, flow cytometry is used to identify the lineage of leukemic blood cells or to classify a lymphoma or leukemia as either T or B cells, which provides prognostic information of the disease. It also examines functions of natural killer cells and T-cell, which have shown some correlation with psychological distress of patients.

Flow cytometry is used for assessment of the affected lymphoid tissue which is important for staging and classification of malignant lymphomas. It is also used in laboratory diagnosis of immune-mediated cytopenias, like hemolytic anemia, thrombocytopenia and neutropenia, etc. Moreover, its sensitivity is more in comparison to conventional direct agglutination test (e.g., Coombs for immune-mediated hemolytic anemia [IMHA]). It is also used to monitor the progression of acquired immunodeficiency syndrome (AIDS) in humans with human immunodeficiency virus (HIV).

CONCLUSION

To summarize, in the current scenario, flow cytometry forms an integral part of diagnosis, especially in hematolymphoid malignancies. It further aids in conducive disease management by guiding therapeutic protocols. Due to the accuracy and precision of this technique and its ability to use samples obtained from minimally invasive methods, like peripheral blood sampling, it is also widely used in assessing the response of the patient to treatment regimens. As of date, it can be said to be indispensable to the laboratory. In the times to come, FCMs can be expected to continue to decrease in energy consumption as well as size and increase in detection and precision measurements.

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The Role of Zinc in Antiviral Immunity

A recent article published in *Advances in Nutrition* discussed that zinc is an essential trace element that is crucial for growth, development and maintenance of the immune function. This micronutrient influences all organs and cell types, representing an integral component of approximately 10% of the human proteome and encompassing hundreds of key enzymes and transcription factors. However, zinc deficiency is common, affecting up to a quarter of the population in the developing nations, but also affecting distinct populations in the developed world—as a result of lifestyle, age and disease-mediated factors. Therefore, zinc status is a critical factor that can influence antiviral immunity, especially, as zinc-deficient populations are often most at risk of acquiring viral infections such as HIV or hepatitis C.

The authors stated that evidence of over the past 50 years demonstrate the antiviral activity of zinc against a variety of viruses and *via* numerous mechanisms. The therapeutic use of this trace element for viral infections, such as herpes simplex and the common cold, has stemmed from these findings.

The tight regulation of zinc homeostasis both systemically and intracellularly indicates that zinc plays an essential role in human health. Although zinc is a component of ~10% of the human proteome, zinc in different forms (free compared with protein-bound) can stimulate a variety of signaling events, including the antiviral response – rendering a direct antiviral, as well as a stimulant of antiviral immunity. The article reported that *in vitro* studies have suggested that free zinc may possess potent antiviral effects, and this evidence is supported by trials of creams, lozenges and supplements with high free zinc content.

Scientists postulate that zinc-binding proteins, such as the metallothioneins, may possess antiviral roles. Zinc treatment applied at a therapeutic dose and in the right form has the potential to drastically improve the clearance of both chronic and acute viral infections, as well as their accompanying pathologies and symptoms. The role of zinc as an antiviral can be categorized as – zinc supplementation implemented to improve the antiviral response and systemic immunity in patients with zinc deficiency and zinc treatment performed to specifically inhibit viral replication or infection-related symptoms.

Source: Read SA, Obeid S, Ahlenstiel C, et al. Adv Nutr. 2019;10(4):696-710.

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Burnout Syndrome: A Disease of Modern Era

PARINITA C HAZARIKA*, SMARANIKA CHOUDHURY†, ARUN KUMAR GUPTA‡

ABSTRACT

Burnout syndrome (BOS) is recognized worldwide as a major challenge to workers' health and the functioning of their organizations. It is a work-related constellation of symptoms that usually occurs in individuals without any prior history of psychological or psychiatric disorders. The trigger is the discrepancy between the expectations and ideals of the employee and the actual requirements of their position. It occurs most amongst professional people in the caring professions of medicine, nursing, social work, counseling and teaching whose work involves constant demands and intense interactions with people who have physical and emotional needs. According to the most common description at present, burnout syndrome is characterized by exhaustion, depersonalization and reduced satisfaction in performance. This article gives an overview of the current scenario for burnout syndrome. By examining diagnostic criteria and possible therapies, methods of prevention are discussed.

Keywords: Burnout syndrome, healthcare professionals, chronic stress, exhaustion, depersonalization

Burnout is a global concern and work-related stress has the potential to negatively affect the individual's psychological and physical health and therefore affects the organization's effectiveness. Thus, it is recognized worldwide as a major challenge to workers' health and the functioning of their organizations. Several epidemiological studies have found a high prevalence of the professional stress syndrome of burnout in western and developing countries.[1] Burnout is usually assessed in an occupational setting and most occupational groups, white-collar (civil servants), blue-collar (manual workers) and the 'helping' professions (healthcare workers, caregivers and teachers) may be affected.[2,3] Nevertheless, burnout syndrome (BOS) occurs mainly among professionals whose work involves constant demands and intense interactions with people who have physical and emotional needs. The term 'burnout' was coined in the USA over 2 decades ago. The psychoanalyst Freudenberger, for example, published one of the first scientific descriptions of the BOS as psychiatric and physical breakdown.[4] In 1981, Maslach introduced a further reaching definition and an instrument for measuring burnout which is still the most frequently used today, the Maslach Burnout Inventory (MBI).[5,6]

BOS is a work-related constellation of symptoms that usually occurs in individuals without any prior history of psychological or psychiatric disorders. BOS is triggered by the discrepancy between the expectations and ideals of the employee and the actual requirements of their position.

RISK FACTORS

Negative job characteristics

- Workload: overwork and heavy workload, boredom
- Work conflicts
- Diminished resources
- Lack of input or feedback
- Job insecurity
- Effort-reward imbalance
- Length of training and delayed gratification

Occupational factors

- Step hierarchy
- Understaffing
- High demands for employees
- Number of years in current profession and total number of years

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Organizational factors

- Continuing rapid organizational changes

Demographic variables

- Younger adults
- Unmarried people/women caring for children

Personality traits

- Low hardiness
- Poor self-esteem

Job attitudes

- Unrealistically high expectations
- Financial issues (salary).

EPIDEMIOLOGY

Burnout can occur in any occupation.[7] However, it has been found to occur most amongst professional people in the caring professions of medicine, nursing, social work, counseling and teaching. When studied, the prevalence amongst healthcare workers approaches 25%.[8]

Phases

Psychologists Herbert Freudenberger and Gail North have theorized that the burnout process can be divided into 12 phases, which are not necessarily followed sequentially.

1. **The compulsion to prove oneself:** Often found at the beginning is excessive ambition. The desire to prove oneself in the workplace turns into compulsion.
2. **Working harder:** In order to meet the expectations, they tend to focus solely on work, while they take on more work than they otherwise would. It may happen that they become obsessed with doing everything themselves to show that they are irreplaceable.
3. **Neglecting their needs**: Since, they have to devote everything to work, they now have no time and energy for anything else.
4. **Displacement of conflicts:** They become aware that what they are doing is not right, but they are unable to see the source of the problem.
5. **Revision of values**: While falling into a state of denial of basic physical needs, perceptions and value systems change. Work consumes all energy, leaving none for friends and hobbies.
6. **Denial of emerging problems:** People may become intolerant and dislike being social. They may be seen as aggressive and sarcastic.
7. **Withdrawal**: Minimal social contact turns into isolation. Even alcohol or drugs may be used as a release from obsessive working.
8. **Obvious behavioral changes:** Co-workers, family, friends and others in their immediate social circles cannot overlook the behavioral changes in these people.
9. **Depersonalization:** It is possible that they no longer see themselves or others as valuable. Their view of life narrows to only seeing the moment and life turns into a series of mechanical functions.
10. **Inner emptiness.**
11. **Depression.**
12. **Burnout syndrome.**

They collapse physically and emotionally and need immediate medical attention. In extreme cases, suicidal ideation may occur.

SIGNS AND SYMPTOMS

Burnout is considered to have a range of symptoms. It is a state of chronic stress that leads to:

- Physical and emotional exhaustion
- Cynicism and detachment
- Feelings of ineffectiveness and lack of accomplishment.

However, burnout does not happen suddenly. Its nature is much more insidious, creeping up on us over time like a slow leak, which makes it much harder to recognize. Still, our bodies and minds do give us warnings, and if we know what to look for, we can recognize it before it is too late.

WHAT ARE THE SIGNS OF BURNOUT?

Each of the three areas described above is characterized by certain signs and symptoms (although there is overlap in some areas). These signs and symptoms exist along a continuum.

Signs of Physical and Emotional Exhaustion

- **Chronic fatigue**
- **Insomnia**
- **Forgetfulness/impaired concentration and attention**

- **Physical symptoms:** Physical symptoms may include chest pain, palpitations, shortness of breath, gastrointestinal pain, dizziness, fainting and/or headaches.
- **Increased illness**
- **Loss of appetite**
- **Anxiety**
- **Depression**
- **Anger**.

Signs of Cynicism and Detachment

- **Loss of enjoyment.**
- **Pessimism:** At first, this may present itself as negative self-talk and/or moving from a glass half-full to a glass half-empty attitude. At its worst, this may move beyond how we feel about ourselves and extend to trust issues with co-workers and family members and a feeling that we cannot count on anyone.
- **Isolation:** In the later stages, this may seem like mild resistance to socializing. In the latter stages, we may become angry when someone speaks to us, or we may come in early or leave late to avoid interactions.
- **Detachment:** Detachment is a general sense of feeling disconnected from others or from our environment. It can take the form of the isolative behaviors described above.

Signs of Ineffectiveness and Lack of Accomplishment

- **Feelings of apathy and hopelessness:** This is similar to what is described in the depression and pessimism sections of this article.
- **Increased irritability.**

HOW IS BURNOUT DIAGNOSED?

There are no well-researched methods to diagnose burnout yet. Various questionnaires can be used for self-assessment. The problem with these questionnaires is that there is no common definition of what burnout is. The most common questionnaire is the "Maslach Burnout Inventory" (MBI), which is available for different professional groups. This questionnaire was not developed for clinical practice, but for scientific research on burnout. The MBI is by far the most widely used, accepted, valid and reliable measurement tool of stress and burnout. The 22 total items are broken up into the three themes with nine items relating to emotional exhaustion, five to depersonalization and eight to accomplishment. Each item is also rated on a frequency and intensity scale. The frequency scale ranges from zero (never) to six (everyday). The intensity scale ranges from one (never) to six (very-strong).

Generally, symptoms said to be a result of burnout can also have other causes, for example mental or psychosomatic disorders like depression, anxiety disorders or chronic fatigue syndrome. So, it is important to look for possible causes and not to think of 'burnout' straight away. Otherwise there is a risk of using wrong or ineffective treatments.

HOW TO RECOVER FROM (OR PREVENT) BURNOUT?

The first and most important step in preventing or recovering from burnout is to recognize the problem and objectively survey the situation.

Stop (or at least Slow Down)

If we are working 50 or more hours a week, cutting that number to the bare minimum helps. If possible, availing of sick days, working from home once a week and taking a vacation or a leave of absence will give ourselves the time needed to decompress, reflect and reconnect.

Communicate

When in doubt, there is a need to seek counsel and support from family, friends and industry peers.

Set Boundaries and Expectations

The days of the 9-to-5 jobs are gone and the boundaries between work and home are blurred to the point of nonexistence. We are expected to be available nearly all the time, and the problem is often exacerbated for freelancers or anyone who works primarily from a home office, where the only divide between being 'at home' and being 'at work' is a single door or a flight of stairs.

Sleep More

Sleep gives our brains a chance to work out problems and process the information we have absorbed throughout the day. Even if we can function on 4 or 5 hours of sleep, how much better would we function on 7 or 8 hours?

Create a Daily Routine

It is not unusual for creative types to do their best work at the same time every day. By this, it means that it is important to follow our own circadian rhythms.

It is recommended that the most important work (or the work requiring the greatest focus) be done during that time when we are most energized and have the fewest distractions.

Make Time for Numero Uno

Spending time with family, friends or your personal interests may provide the fulfilment, which we don't get at work.

Examine Your Values, Goals and Measures of Success

To know ourselves. What are we passionate about? How do we evaluate ourselves against expectations placed on us by managers and clients, and the work we are doing? Are these measures grounded in reality? Are our personal development goals being met by the type of work we are doing? Are we feeling too much pressure from unrealistic demands or those that go against our values? What frustrates us?

Simply connecting with things that matter to us can provide perspective.

Focus

Good work requires focus. Modern communication conveniences provide us a valuable social connection to the outside world, but they can also destroy our concentration and clarity.

Change Your Situation

Changing departments, learning a new skill or simply focusing more on the things we are good at, can make us happy.

Rely on a Good Process

If we already have a process that we think works on talking to our peers, reading up on the topic, seeing what processes others use, experimenting and finding out what works for us, we can scrutinize, clarify and simplify it as much as possible.

Regaining Your Balance

When we are burned out, we know it. The process often begins with a look inward to learn what gives our life balance, such as family, friends, personal interests and hobbies—the things that counterbalance our life on the web. If our waking hours are entirely consumed by our work, or if we are unfocused and inattentive to our own needs, burnout will be waiting at every turn of our life.

RESEARCH

The intensive care unit (ICU) is a highly stressful environment and may therefore be associated with a high rate of BOS in staff members.[9,10] The cost of BOS includes decreased quality of care, absenteeism and high turnover rates and poor communication with families. A large multicenter study of the prevalence of severe BOS in ICU nursing staff members was conducted in France as measured by the MBI scale for human service professionals (Questionnaire Survey). Among 278 ICUs contacted for the study, 165 (59.4%) included 2,525 nursing staff members, of whom 2,392 returned questionnaires with complete MBI data. Of the 2,392 respondents (82% female), 80% were nurses, 15% nursing assistants and 5% head nurses. Severe BOS-related symptoms were identified in 790 (33%) respondents.[11]

Burnout is frequent among physicians with rates ranging from 25% to 60%, depending on the working conditions and medical speciality. Studies of burnout in practicing physicians have shown that burnout can develop at any stage in the career of a physician. In a study focused on internal medicine residents, 76% of respondents met a high level of BOS. Determinants of burnout consist of job characteristics, demographic variables (sex, age) and personality traits.[12]

Many aspects of professional practice have changed for both doctors and nurses and include lack of autonomy, decreased resources and the requirement of a high level of competence and technical support. Workload, stressful work environments like ICUs, severity of illness and conflicts with co-worker or with patients, may be risk factors for BOS.

CONCLUSION

In the light of social change and a transformation in the work situation, interest in the problem of burnout has grown over the past decade. There is a conspicuous discrepancy; however, between what is regarded as certain knowledge and what is published opinion. To date, there is no generally accepted definition of burnout, or binding diagnostic criteria. According to the most common description at present, BOS is characterized by exhaustion, depersonalization and reduced satisfaction

in performance. Because of its etiopathogenesis, burnout is today mainly regarded as the result of chronic stress, which has not been successfully dealt with. This paper gives an overview of the current scenario for BOS. By examining diagnostic criteria and possible therapies, methods of prevention are discussed. There is an urgent need for further investigations to deal with BOS as a work-related disease.

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Severe or Fatal COVID-19 Very Rare in Children

Children and young people have lesser likelihood, compared to adults, of getting severe cases of coronavirus disease 2019 (COVID-19) infection, and death from the disease among children is very rare, suggests research from UK.

According to the study of COVID-19 patients admitted to 138 hospitals in Britain, less than 1% were children, and of those, less than 1% died, all of whom were already having a serious illness or underlying health disorders. Malcolm Semple, Professor of Outbreak Medicine and Child Health at Britain's University of Liverpool, stated that COVID-19, in itself, is not harming children on a significant level. The study is published in the *BMJ*… (*Reuters*)

FDA Expands Emergency Use Authorization for Remdesivir

The US Food and Drug Administration (FDA) has expanded the scope of the current emergency use authorization (EUA) for remdesivir for COVID-19 treatment. The expanded EUA now includes treatment of all hospitalized patients, adult and pediatric, with suspected or laboratory-confirmed COVID-19, regardless of disease severity.

In May 2020, the FDA had issued an EUA authorizing the drug for the treatment of hospitalized adult and pediatric patients with severe COVID-19. The initial EUA included patients with low blood oxygen levels or those requiring oxygen therapy or more intensive breathing support such as a mechanical ventilator.

The FDA, based on its review, has now concluded that it seems acceptable that remdesivir may be effective for the treatment of suspected or laboratory-confirmed COVID-19 in all hospitalized patients… (*FDA*)

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Lipoprotein(a) – A Potential Cardiovascular Risk Factor and Therapeutic Approaches

PRAGATI KAPOOR*, PANKAJ KUMAR†, AK KAPOOR‡

ABSTRACT

Lipoprotein(a), also called as Lp(a), has been shown to be an independent, causal, genetic risk factor for cardiovascular disease and aortic stenosis by genetic and numerous epidemiological studies. High Lp(a) level is an important risk factor for coronary heart disease, cerebrovascular disease, atherosclerosis, thrombosis and stroke. The physiological functions, the mechanism and sites of Lp(a) catabolism, and pathophysiological details are not well-understood though several mechanisms of Lp(a) participation in atherogenesis have been proposed. The goal of therapy is to bring down elevated Lp(a) levels to below 50 mg/dL. Both statins and estrogens are not used for therapy of elevated Lp(a) levels. Niacin and aspirin are two relatively safe, easily available and inexpensive drugs, which significantly reduce raised Lp(a) levels. A variety of other medications that are in various stages of development are dealt with including miscellaneous agents whose role has not been clinically verified.

Keywords: Lipoprotein(a), atherogenesis, therapeutic approaches

Lipoprotein(a) [also called as Lp(a) or LPA] is a lipoprotein subclass. Lipoprotein is an independent, causal, genetic risk factor for cardiovascular disease (CVD).[1] Genetic studies and numerous epidemiological studies have also identified Lp(a) as a risk factor for atherosclerotic diseases such as coronary heart disease (CHD) and stroke.[2-5] Lp(a) was discovered in 1963 by Kare Berg.[6] Interestingly, Lp(a) is present only in humans, apes and old world monkeys.

STRUCTURE

The chemical structure of Lp(a) consists of a low-density lipoprotein (LDL)-like particle and the specific apolipoprotein (a) [apo(a)], which is covalently bound to the apoB-100 of the LDL-like particle via one disulfide bridge.[7,8] Thus, Lp(a) is composed of apoB-100 and apo(a). Lp(a) is a spherical macromolecular complex with a diameter of approximately 25 nm, and density ranging from 1.05 g/mL to 1.12 g/mL.[7] Its concentrations are not significantly affected by dietary or environmental effects. Lp(a) plasma concentrations are highly heritable and mainly controlled by the apo(a) gene (LPA) located on chromosome 6 q 26-27. Probably, LPA gene may be responsible for 91% of the variation in Lp(a) concentration; of these 69% are due to the number of kringle IV (KIV) type 2 repetitions. Lp(a) plasma concentration ranges from <1 mg to >1,000 mg/dL. It is worth mentioning that individuals without Lp(a) or with very low Lp(a) levels seem to be healthy.

Apo(a) proteins vary in size due to a size polymorphism (KIV-2 VNTR), which is caused by a variable number of so called KIV repeats in the LPA gene. This size variation at the gene level is expressed on the protein level as well, resulting in apo(a) proteins with 10 to >50 KIV repeats.[8,9] These variable apo(a) sizes are known as apo(a) isoforms. Generally, there is inverse correlation between the size of the apo(a) isoforms and the Lp(a) plasma concentration.[10] As smaller apo(a) isoforms can be generated more quickly per unit time, hence small isoforms are associated with higher plasma Lp(a) levels. Age and sex have little influence on Lp(a) levels, though racial factor has an important influence on Lp(a) levels. The half-life of Lp(a) in the circulation is about 3-4 days. There are 6 different alleles for Lp(a). The protein apo(a) is highly homologous (similar) to

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plasminogen, one of the proteins of the fibrinolytic system, though apo(a) has important differences compared with plasminogen.

SYNTHESIS AND METABOLISM

The synthesis and metabolism of Lp(a) have not been completely clarified and are totally independent from LDL synthesis and metabolism in spite of structural similarities between Lp(a) and LDL. Lp(a) is synthesized in the liver. Apo(a) is expressed by liver cells (hepatocytes). There is no coordination between the synthetic pathways of apo(a) and of apoB-100, as there is no coordination between synthesis of Lp(a) and of plasminogen, its structural analog.[7] Further, Lp(a) levels are not related to lipoprotein lipase activity.

The mechanism and sites of Lp(a) catabolism are also not well-defined. Moreover, the way cellular uptake occurs is also not well-established.[7] Uptake via LDL receptor is not a major pathway of Lp(a) metabolism[11] and the role of LDL receptor or isoforms size in that process is limited since only a small fraction of Lp(a) binds to hepatoma cells via LDL receptors. Probably, kidneys may play a role in Lp(a) clearance from plasma.[12] Other receptors, such as asialoglycoprotein receptors, megalin receptors and macrophage scavenger receptors may be involved in Lp(a) uptake.[13]

METHODOLOGY TO DETERMINE LP(a)

Lp(a) is commonly estimated by determining the apo(a) concentration by using monoclonal anti-apo(a) antibodies. It may be mentioned, there are difficulties in standardizing the methodology to determine Lp(a) for accurate comparison between different studies. Presently, there are a variety of methods for determining Lp(a). A standardized reference material accepted by the World Health Organization (WHO) Expert Committee on Biological Standardization and the International Federation of Clinical Chemistry and Laboratory Medicine has been notified towards standardizing results. Moreover, a test with simple quantitative results may not provide a complete assessment of risk. Therefore, these assays must be validated with reference standard.

Lipoprotein(a) - Lp(a):

- Desirable: <14 mg/dL
- Borderline risk: 14-30 mg/dL
- High risk: 31-50 mg/dL
- Very high risk: >50 mg/dL.

Lp(a) Concentration and Populations

The racial factor has an important influence on Lp(a) levels. There is two- to three-fold higher Lp(a) plasma concentration in populations of African descent compared to Asian, Oceanic or European populations,[14] but these levels are not related to coronary artery disease (CAD) in Africans.

Physiological Function

The physiological function of Lp(a)/apo(a) is still unknown. The data till date did not show a physiological function for Lp(a) in lipid transportation or metabolism regulation.[7] Its role within the coagulation system seems plausible owing to high similarity between apo(a) and plasminogen.[8] Apo(a) has potent lysine binding domains similar to those on plasminogen and binds to damaged endothelial cells and exposed or injured subendothelial matrix proteins, delivers cholesterol for cell membrane growth. The other functions may be related to recruitment of inflammatory cells through interaction with Mac-1 integrin, angiogenesis, wound healing, innate immunity and infection.

Pathophysiology

There are 4 major categories of lipid abnormalities in human beings:[1] a) A raised LDL cholesterol, b) a low high-density lipoprotein (HDL) cholesterol, c) elevated triglycerides and d) elevated Lp(a). Of these, LDL cholesterol, HDL cholesterol and triglyceride levels are modulated by diet. In contrast, Lp(a) plasma levels are mediated largely by the LPA gene locus present on chromosome 6 q 22-23 and is minimally affected by diet.[15]

Presently, Lp(a) remains conceptually only a 'pathogenic lipoprotein.' Lp(a) level >50 mg/dL is typically considered to be elevated for clinical biomarkers. Transient increases in Lp(a) levels are noted in the presence of inflammatory processes or tissue damages, such as those occurring with other acute phase proteins (haptoglobin, α_1-antitrypsin and C-reactive protein).[15] This can be seen with an episode of acute myocardial infarction, wherein Lp(a) levels are considerably increased in first 24 hours, returning to base values in approximately 30 days. Lp(a) levels are also increased in chronic inflammatory disease, such as rheumatoid arthritis, systemic lupus erythematosus and acquired immune deficiency syndrome and following heart transplantation, pulmonary arterial hypertension and chronic renal failure.[16] In contrast, liver diseases and abusive use of steroid hormones decrease Lp(a) levels.[16] The relationship between Lp(a) and diabetes has not

been well-defined. Contrary views have been expressed in type 1 diabetes mellitus. Similarly, conflicting results have been reported for type 2 diabetes as well.

Lp(a) concentrations have a hereditary character, tending to remain constant throughout the life and are not altered by environmental factors. Elevated Lp(a) level is a risk factor for CHD, CVD, atherosclerosis, thrombosis and stroke, though, association between Lp(a) levels and stroke is not as strong as that between Lp(a) and CVD.[2]

Several mechanisms have been proposed for Lp(a) participation in atherogenesis. The structure of Lp(a) is similar to plasminogen and tissue plasminogen activator (tPA); it might lead to interference with fibrinolysis cascade since it competes with plasminogen for its binding site, causing reduced fibrinolysis. Lp(a) stimulates secretion of plasminogen activator inhibitor-1 (PAI-1), it leads to thrombogenesis. Lp(a) also carries cholesterol and thus contributes to atherosclerosis.[17] The mechanisms linking thrombogenesis and atherogenesis with plasma lipoproteins via Lp(a) have thrilled the scientific community.

The probable sequence of events is as follows: Lp(a) would interfere with fibrinolytic system thus Lp(a) competes with plasminogen for binding sites of endothelial cells, inhibiting fibrinolysis and promoting intravascular thrombosis.[18] Additionally, Lp(a) transports the more atherogenic proinflammatory oxidized phospholipids, which attract inflammatory cells to vessel walls,[19,20] and leads to smooth muscle cell proliferation.[21] Probably, the major effect of Lp(a) is on advanced plaque development and destabilization rather than thrombosis.[1]

An elevated Lp(a) is clearly proatherogenic.[22] The participation of Lp(a) in atherogenesis could be multifaceted. One mechanism of atherogenicity is through the LDL component. However, apo(a) alone and Lp(a) as lipoprotein have additional potential contributions,[23] including increasing endothelial cell permeability and expression of adhesion molecules, promoting smooth muscle cell proliferation, enhancing monocyte entry and retention in the vessel wall, macrophage foam cell formation, promoting release of proinflammatory interleukin (IL)-8 levels, and antifibrinolytic effects, as a carrier of proinflammatory and proatherogenic oxidized phospholipids (OxPL).[24] A study has reported that Lp(a) and OxPL mediate macrophage apoptosis in endoplasmic reticulum. Since, macrophage apoptosis is a key component of plaque vulnerability, these data provide supporting evidence of Lp(a) as a risk factor for the development of advanced, clinically relevant atherosclerotic lesions.[1] Lp(a) levels also predict severity of coronary atherosclerosis in clinically symptomatic patients. A key component of atherogenicity of Lp(a) has been the contribution of OxPL. OxPL are immunogenic and accumulate in atherosclerotic lesions and mediate plaque destabilization. Thus, raised OxPL on apoB are linked with the presence and progression of CAD and peripheral artery disease (PAD) and predict new CVD events in prospective studies.[1]

Another proatherogenic mechanism relates to direct deposition of Lp(a) on arterial wall similar to that which happens with LDL and oxidized LDL as Lp(a) is more prone to oxidation than LDL.[7] This might facilitate uptake of macrophages via scavenger receptor.[13] This is the most universal mechanism of atherogenesis. Yet, another proatherogenic mechanism of Lp(a) refers to the inverse correlation between lipoprotein levels and vascular reactivity, wherein increase in Lp(a) plasma levels will induce endothelial dysfunction.[25]

A prime feature of atherosclerosis is chronic inflammation and accumulation of proinflammatory substances in the vessel wall, modified and oxidized products of apoB-containing lipoprotein, are key mediators of such proinflammatory responses that contribute to clinical manifestations of CVD. Helgadottir et al[26] has observed the independent residual risk of Lp(a) in mediating CVD is substantial and this can provide an opportunity and a potential target of therapy in reducing the overall risk of CVD even further. Helgadottir et al have suggested that LPA variants rs 10455872 and rs 3798220, defined as LPA risk score by combining their effects, are associated with angiographically determined earlier onset of CAD ($p = 4.8 \times 10^{12}$), PAD ($p = 2.9 \times 10^{14}$), aortic aneurysm ($p = 6.0 \times 10^{5}$) and ischemic stroke subtype large artery atherosclerosis ($p = 6.7 \times 10^{4}$).

Further, investigators have observed associations between Lp(a) and inflammatory cytokines, such as tumor necrosis factor-alpha (TNF-α), transforming growth factor-beta (TGF-β), IL-6 and monocyte chemoattractant protein-1 (MCP-1).[27,28] In addition to a reduction in fibrinolysis, it may involve platelet aggregation, induction of the expression of adhesion molecules, vascular remodeling via changes in the proliferative and migratory capacity of endothelial cells and resident smooth muscle cells, oxidative modification and formulation of foam cells.[7] In brief, Lp(a) may be atherothrombotic through its LDL moiety, but also through apo(a), including its ability to be retained in vessel well and mediate proinflammatory and

proapoptopic effects including those potentiated by its content of OxPL, and antifibrinolytic effects.[1]

Lp(a) as Cardiovascular Risk Factor

A number of cross-sectional studies have confirmed the association between Lp(a) levels and risk of developing CAD, regardless of 2.3 times higher in patients with Lp(a) levels over 50 mg/dL. Riches et al[28] noted risk as twice greater for Lp(a) levels over 20 mg/dL. Rhoads et al[29] and Murai et al[30] confirmed the relationship between Lp(a) and CAD and cerebral infarction. Rhoads et al[29] also noted that with advancing age the risk decreased, and in the age group over 70 years risk became 1.2 times. In the Brazilian population, Maranhao et al,[31] have reported a risk of developing CAD 2.3 times greater when Lp(a) levels were over 25 mg/dL. In Korean population with CAD, a raised Lp(a) has been labeled as an independent risk factor.[32] A meta-analysis of 27 prospective studies has clearly identified an independent association between Lp(a) and CAD.[5] A Danish prospective study involving more than 9,000 individuals over 10 years follow-up has observed that very high Lp(a) levels (≥120 mg/dL) increased 3 to 4 times the risk of CAD.[33]

Most studies and meta-analyses have shown an increase in CVD risk starting at Lp(a) >25 mg/dL. A majority of prospective studies reported Lp(a) is really an independent risk factor for CVD though conflicting results, ranging from strong positive associations to complete lack of association between Lp(a) and CVD are in the literature. Yet, high Lp(a) levels enhanced the potency as risk factors of both hypercholesterolemia and low HDL cholesterol concentration.[34] High Lp(a) levels predict risk of early atherosclerosis independently of other cardiac risk factors, including LDL. In patients of advanced CVD, Lp(a) indicates a coagulant risk of plaque thrombosis. Elevated Lp(a) levels may augment the CHD risk from increased LDL cholesterol concentrations as has been demonstrated in patients with familial hypercholesterolemia.[35] A consensus paper issued by the European Atherosclerosis Society in 2010 describes Lp(a) as a causal risk factor for CHD and CVD. The possibility that Lp(a) may become functionally altered in patients with CAD has been put forward by Tsironis et al[36] on the basis of mass and specific activity of Lp(a) as mediator of platelet-activating factor acetylhydrolase activity, an enzyme that hydrolyzes oxidized phospholipids. The mean Lp(a) concentrations are markedly high in black individuals, 2 to 3 times greater than in Caucasian and Oriental individuals,[14] but these levels are nonpredictive of CVD in black individuals.

Additionally, high Lp(a) is also a risk factor for atherosclerosis in other arterial beds, such as in ischemic cerebral disease where risk gets escalated with Lp(a) levels, over 30 mg/dL. Further, in a 13-year long follow-up in 14,000 participants, a prospective study has shown a higher incidence of ischemic cerebral disease with raised Lp(a) level.[37] Similarly, in another study involving 50,000 individuals, it was also shown that a raised Lp(a) level is associated with ischemic cerebrovascular accidents.[5] In a meta-analysis of 40 prospective studies involving 58,000 individuals, a 2 times increase in the risk for developing CAD and cerebrovascular accident was noted in individuals with smaller apo(a) isoforms, regardless of the Lp(a) concentration and classical risk factors.[38] In recent years, a number of studies have reported that elevated Lp(a) levels are independently and linearly predictive of future CVD, though the mechanisms linking Lp(a) to atherogenesis are still unclear and that studies proving the therapeutic decrease of Lp(a) reduces the number of events still lack. The influence of Lp(a) levels on carotid intima-media thickness is still controversial. An inverse association in Japanese population has been observed while no relationship between that thickness and Lp(a) levels has been noted in Spaniards.

Regarding implication of gender, it was observed that a raised lipoprotein level leads to more significant risk repercussions in female sex compared to male sex.[39] A more recent Atherosclerosis Risk in Communities (ARIC) study has reported differences in LP(a) concentrations between sexes, which is higher in females.[40] Although most studies have shown no difference between sexes in Lp(a) concentrations. In postmenopausal women, an elevated Lp(a) and triglyceride level are predictive of the presence of CAD. Investigators have observed that predictive utility of Lp(a) is markedly attenuated among women taking hormone replacement therapy and that the relationship of high Lp(a) levels with increased CVD is modified by hormone replacement therapy.[41]

Atherogenesis is a common causal factor of abdominal aortic aneurysm and Lp(a) levels are elevated in abdominal aneurysm showing the association between lipoprotein and atherogenesis. Recent events suggest that genetic variation in the LPA locus-mediated by Lp(a) concentration may also predict aortic valve stenosis.[42] This can well explain why heart valve calcification may run in families. A causal relationship between Lp(a) and calcific aortic valve disease has also been demonstrated. Nongenetic risk factors for aortic valve calcification include advanced age, high blood

pressure, obesity, high cholesterol levels and smoking. Development of novel targeted medications in future might slow the progression of disease. Statins have not been shown to reduce aortic valve calcification.

High Lp(a) levels predict risk of early atherosclerosis independently of other cardiac risk factors, including LDL and that Lp(a) concentrations also associate significantly with the severity of coronary atherosclerosis. In addition, Lp(a) appears to be an independent risk factor in both primary and secondary settings though there is a paucity of information on the predictive value of Lp(a) in patients with stable CVD.[43] The authors observed that Lp(a) represents a significant risk factor for recurrent events. In patients of advanced CVD, Lp(a) indicates a coagulant risk of plaque thrombosis. In the Long-term Intervention with Pravastatin in Ischemic Disease (LIPID) study, baseline Lp(a) was associated with future CVD and CHD. The authors observed that baseline Lp(a) concentration was associated with total CHD events ($p < 0.001$), total CVD events ($p = 0.002$) and coronary events ($p = 0.03$). For events after 1 year, an increase in Lp(a) at 1 year was associated with adverse outcomes for total CHD events and total CVD events ($p = 0.002$ each). It was demonstrated that a rising Lp(a) level is associated with cardiovascular events.[43]

THERAPEUTIC APPROACHES FOR ELEVATED LP(a) LEVELS

The European Atherosclerosis Society currently recommends that patients with a moderate or high risk of cardiovascular risk having one of the following risk factors such as premature CVD, familial hypercholesterolemia, family history of premature CVD, family history of elevated Lp(a), recurrent CVD despite statin treatment, ≥3% 10-year risk of fatal CVD according to the European guidelines, ≥10% 10-year risk of fatal and or nonfatal CVD according to US guidelines should be screened for their Lp(a) levels.[2]

If the Lp(a) levels are raised, treatment should be started with a goal of bringing the level below 50 mg/dL. In addition, the patient's other cardiovascular risk factors (including LDL levels) should be optimally managed.[2] Besides Lp(a) plasma concentration, the apo(a) isoforms might be an important risk parameter as well. Moreover, a better understanding of the basic mechanism of production and metabolism of Lp(a) and apo(a) is important to correlate the effect of future therapeutic agents. Major gaps in clinical medicine are: Lowering Lp(a) levels leads to clinical benefit have not been documented; in majority of studies, Lp(a) levels were lowered in conjunction with changes in other lipoprotein thus complexing the outcomes and the underlying mechanisms of Lp(a)-lowering of these agents are not fully clarified.[1]

EFFECTS OF DRUGS ON LP(a) CONCENTRATION

There is no specifically targeted definitive therapy to decrease Lp(a) levels and specific and effective agents do not exist without affecting other lipoproteins. Traditional lipid-lowering agents such as statins or fibrates do not consistently decrease Lp(a) concentrations. Statins either have no effect or increase Lp(a) levels, sometimes significantly. The use of atorvastatin at a dose of 20 mg/day for 24 weeks caused no effect on Lp(a) levels. In a double-blind study with placebo, using doses of 10 or 40 mg/day of atorvastatin for 12 weeks, the Lp(a) concentration had significantly decreased.[44] A meta-analysis published in 2012, suggests that atorvastatin may lower Lp(a) levels.[45] In respect to lovastatin, simvastatin and gemfibrozil, the latter has shown greater efficacy in reducing Lp(a).[46] Ezetimibe decreases Lp(a) levels approximately 29%;[47] however, ezetimibe is commonly used with simvastatin, which does not have any additive effect to that of ezetimibe in regard to Lp(a) levels.

Presently, more commonly simple treatment which is relatively safe and independent for raised Lp(a) levels is niacin and aspirin.

Niacin

High dose niacin 1-3 g/day generally in an extended-release form is preferred. The Lp(a) levels are reduced by 20-30%,[48] while 4 g/day of niacin leads to 38% reduction in Lp(a) levels though at lower dose 1 g/day niacin has not shown that effectiveness. High dose niacin is widely used in the treatment of dyslipidemia because in addition to reducing LDL cholesterol levels, it increases HDL cholesterol levels and decreases Lp(a) levels.[49] The European Atherosclerosis Society Consensus Panel have suggested use of niacin for Lp(a) and CVD risk reduction. Further, extended-release niacin has also reduced Lp(a) levels in diabetic patients with dyslipidemia. Etofibrate, a hybrid drug combining niacin and clofibrate, at a dose of 1 g/day decreases Lp(a) levels by 26% in type II dyslipidemic patients.[50] Patients with type IIa and IIb hyperlipidemia being treated with neomycin alone have seen a decrease in Lp(a) concentration by 24%, while the neomycin-niacin association in high doses has resulted in a 45% reduction.[51]

It may be mentioned that high doses of niacin are associated with adverse effects, such as migraine, flushing, diarrhea, vomiting, tachycardia and liver toxicity, though, administration of aspirin 30 minutes prior to niacin can relieve some of these adverse effects.

Aspirin

Another commonly used cheap drug, aspirin may be beneficial. Japanese patients with elevated Lp(a) levels (>300 mg/dL) have shown a 20% reduction in Lp(a) levels even with low doses of aspirin (81 mg/day).[52] Women with high Lp(a) levels and an apo(a) polymorphic allele seem to have benefited more from treatment with aspirin than those who lack that allele.[53] Thus, aspirin has been found useful only in patients that carry the apolipoprotein(a) gene minor allele variant (rs 3798220).[53]

Estrogen Replacement

Estrogens lower Lp(a) up to 30%; although estrogen replacement therapy in postmenopausal women has beneficial effects on Lp(a) and other plasma lipids, yet it is studded with controversies regarding increased risk of certain malignant neoplasias and thromboembolic accidents. At present, estrogen is not indicated for treatment of elevated Lp(a). Tamoxifene and raloxifene have not been shown to reduce levels. The precise underlying mechanisms of Lp(a)-lowering of these agents are not fully defined. A variety of agents belonging to different chemical groups are in various stages of development or undergoing clinical trials that may reduce Lp(a) concentrations and in future may open the doors to new avenues of therapy include:

L-carnitine

It is a combination of L-lysine and ascorbate; it may also reduce LPA levels.[54] A more effective treatment is the Linus Pauling protocol, 6-18 g/day ascorbic acid, 6 g/day L-lysine and 2 g/day L-proline. This protocol may reduce Lp(a) two- to five-fold over a few months.

Thyromimetics

The development of selective thyromimetics having specific liver selectivity (affinity to THRβ isoforms) provide an opportunity for the treatment of dyslipidemia, obesity or for weight loss, nonalcoholic fatty liver disease and may play a role in decreasing Lp(a) levels.[55]

- *Sobetirome,* a selective thyromimetic compound reduced LDL cholesterol by 41% at 100 μg/day and in primates caused increase in oxygen consumption, reduction in body weight and minimal effects on skeletal mass. The agent reduces fat mass without increasing food intake and controls dyslipidemia, without causing deleterious effects on heart or bone mass.[55]
- *KB-141* is another THRβ agonist, which is 10 times more selective for stimulating metabolic rate and 30 times more selective for cholesterol-lowering than for increase in heart rate.[55] KB-141 has been shown to cause weight reduction as well as reduction of cholesterol and Lp(a).[56]
- *Eprotirome:* It is also a THRβ selective compound, causes 40% reduction in total and LDL cholesterol after 14 days treatment probably owing to an increase in bile acid synthesis.[55] In humans, data from a clinical trial of 98 hyperlipidemic patients revealed eprotirome to cause 25% reduction in LDL, apoB, along with 37% decrease in Lp(a) at 100 μg/day after 16 weeks. At 200 μg/day, there was 45% decrease in Lp(a). Triglycerides also decreased significantly. No cardiac, bone or muscle effects were observed, though mild transient elevation in liver enzymes was seen. Moreover, selective thyromimetics may have additive LDL cholesterol-lowering when used in combination with statins in animal models.

Cholesteryl Ester Transfer Protein Inhibitors

These agents reduce risk of atherosclerosis by improving plasma lipid levels. They substantially increase HDL, lower LDL and reverse the transport of cholesterol. A few of these agents namely torcetrapib, dalcetrapib, evacetrapib have failed in clinical trials. However, anacetrapib and TA-8995 had shown encouraging phase II clinical trials results.[57] Cholesteryl ester transfer protein (CETP) inhibitors inhibit CETP, which normally transfer cholesterol from HDL cholesterol to very LDL (VLDL) or LDL. Inhibition of this process results in higher HDL levels and reduces LDL levels. CETP inhibitors do not reduce rates of mortality, heart attack or stroke in patients already taking statins.

Antisense Oligonucleotides to ApoB

Mipomersen, a second-generation antisense oligonucleotide injectable drug approved by the Food and Drug Administration (FDA) to be used in homozygous familial hypercholesterolemia in January 2013, might be a promise to decrease Lp(a) levels.[58] Mipomersen is a polynucleotide of 20 bases that is complementary in sequence to a segment of human apoB-100 mRNA. It specifically binds to apoB-100 mRNA, blocking the

translation of the gene product.[58] A reduction in the synthesis of apoB-100 decreases the hepatic production of VLDL, consequently decreasing circulating levels of atherogenic VLDL remnants, intermediate-density lipoprotein (IDL), LDL and Lp(a) particles.[58] Thus, mipomersen reduces all apoB-containing atherogenic lipoproteins and that it consistently and effectively reduces Lp(a) levels in patients with a variety of lipid abnormalities and cardiovascular risk. It has been demonstrated that a specific antisense oligonucleotide directed to KIV-11 repeats lowers apo(a) mRNA and apo(a) plasma levels by 85% in apo(a) transgenic mice, with minor effects on other lipoproteins. Mipomersen's mode of action differs from traditional enzymes or protein-targeting drugs such as statins. It has no dependency on cytochrome P450 metabolism, hence minimal interaction with statins, ezetimibe, bile acids binding resins or other lipid-lowering medications with which it might be combined. Lp(a) levels are decreased in conjunction with changes in other lipoproteins. However, the safety of its use has not been well-established.

Farnesoid X Receptor Agonists

Farnesoid X receptor (FXR, also referred to as NR1H4) is a member of the nuclear receptor superfamily of ligand-regulated transcription factors that plays critical role in the regulation of bile acid, triglyceride and cholesterol homeostasis. However, its impact on cholesterol homeostasis is less clear. Bile acids, the end-product of cholesterol catabolism, are physiological ligand for FXR. Activation of FXR leads to down-regulation of CYP7A1, the rate limiting enzyme in bile acid synthesis, resulting in reduced cholesterol catabolism. WAY-362450 is a potent synthetic FXR agonist, which decreases serum triglyceride levels with efficacy comparable to fenofibrate. It also reduced serum cholesterol levels via reductions in LDL cholesterol, VLDL cholesterol and HDL cholesterol lipoprotein fractions and may be of clinical utility in the treatment of mixed dyslipidemia. Synthetic FXR ligands have been demonstrated to regulate apolipoprotein CII (apoCII) and apolipoprotein CIII (apoCIII), cofactors involved in lipoprotein lipase (LPL)-mediated lipolysis and down modulate sterol regulatory element-binding protein 1c (SREBP-1c), the master regulator of the triglyceride synthetic pathway. Evans et al[59] demonstrated that orally active FXR ligand WAY-362450 potently lowers serum triglyceride levels and VLDL cholesterol in multiple rodent models of dyslipidemia along with consistent-lowering of circulating serum cholesterol levels. The mechanism of action of WAY-362450 is probably through modulation of genes involved in both lipolysis and lipogenesis.

Anti-proprotein convertase, subtilisin/Kexin type 9 (anti-PCSK-9) inhibitors, monoclonal antibodies, protein responsible for degrading LDL receptor; and anti-tocilizumab antibody, that can block IL-6-signaling are still in experimental phase. In severe cases, such as familial hypercholesterolemia, or treatment-resistant hypercholesterolemia lipid apheresis may lead to dramatic reductions in Lp(a) levels in more than 50% of patients.

Miscellaneous Agents

- **Methotrexate:** An immunosuppressive and anti-inflammatory drug used in the treatment of rheumatoid arthritis, may also reduce Lp(a) levels.[60]
- ***Gingko biloba*** may be beneficial, but has not been clinically verified. Coenzyme Q-10, pine-bark extract and pharmacological amounts of fish oil supplements may be helpful to lower the levels of Lp(a) but none of these are clinically proven.

Interactions

Lp(a) has been shown to interact with calnexin, fibronectin and fibrinogen beta chain.

CONCLUSION

New novel, targeted therapeutic agents that can specifically and definitely reduce Lp(a) plasma concentrations are still being sought. In general, in the absence of well-tolerated drugs that effectively decrease Lp(a) concentrations, levels over 25-30 mg/dL should lead to a more strict control of other risk factors for CAD. However, the presumption that lowering Lp(a) levels leads to clinical benefits such as decreased risk of CVD needs confirmation.

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Zinc Supplementation During the Growing Years

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ABSTRACT

Zinc is an essential mineral perceived by the people today as being of "exceptional biological and public health importance", mainly during prenatal and postnatal development. Zinc deficiency affects about 2 billion people in the developing world and is associated with many diseases. In growing children, it causes growth retardation, delayed sexual maturation, infection susceptibility and mainly diarrhea. Consumption of excessive zinc can cause ataxia, lethargy and copper deficiency.

Keywords: Zinc, zinc metabolism, gastroenteritis, zinc deficiency

ZINC AS AN ESSENTIAL ELEMENT

Zinc is an essential trace element for humans. Zinc is found in nearly 100 specific enzymes. It is "typically the second most abundant transition metal in organisms" after iron and it is the only metal which appears in all enzyme classes. In proteins, zinc ions are often coordinated to the amino acid side chains of aspartic acid, glutamic acid, cysteine and histidine.

There is 2-4 g of zinc distributed throughout the human body. Most zinc is in the brain, muscle, bones, kidney and liver, with the highest concentrations in the prostate and parts of the eye. Semen is particularly rich in zinc, which is a key factor in prostate gland function and reproductive organ growth.

IMPORTANCE OF ZINC FOR GROWING CHILDREN

Zinc is an essential component of the diet and is required for the synthesis of enzymes involved in nucleic acid and protein metabolism, including DNA polymerase, RNA polymerase, alcohol dehydrogenase, carbonic anhydrase and alkaline phosphatase. It is well-known that zinc deficiency may result in diseases such as skin dermatitis and lead to taste disorders. However, the association of zinc deficiency with the pathogenesis of liver disease is less well-understood.

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Importance of zinc in growing children is as follows:

- Vital for growth and cell division
- Vital for fertility
- Vital for the immune system
- Vital for taste, smell and appetite
- Vital for skin, hair and nails
- Vital for vision.

WHO NEEDS ZINC?

The essentiality of zinc in humans was established in 1963. During the past 50 years, tremendous advances in both clinical and basic sciences of zinc metabolism in humans have been observed.

Children and even adults need zinc in sufficient quantities. Children need zinc to grow, adults need zinc for maintenance of optimum health. Growing infants, children and adolescents, pregnant women and lactating mothers, athletes, vegetarians and the elderly often require more zinc.

Barnes and Moynahan (1973) reported a 2-year-old girl with severe acrodermatitis enteropathica who was being treated with diiodohydroxyquinoline and a lactase-deficient synthetic diet but was not showing any satisfactory response to this therapy. The serum zinc concentration was significantly decreased. They, therefore, administered oral zinc sulfate to correct this deficiency. Surprisingly, the skin lesions and gastrointestinal symptoms cleared after zinc supplementation.

A severe deficiency of zinc has also been observed in patients with Wilson's disease who received penicillamine therapy as decoppering agent. This treatment may

induce excessive zinc loss and cause severe deficiency of zinc.

Implications of zinc deficiency in children is discussed in the following section.

ZINC AND GROWTH

Growth is the first limiting effect of zinc deficiency in experimental animals. Zinc deficiency decreases circulating insulin-like growth factor 1 (IGF-1) concentration independent of total energy intake.

In humans, zinc deficiency decreases circulating IGF-1 concentration. IGF-1 receptor possesses tyrosine kinase activity. On activation of the receptor by IGF, a cascade of phosphorylation occurs within the cell leading to regulation of cell cycle and cell division. Tyrosine phosphorylation of the receptor is essential for its activation, and I hypothesize that because zinc has been shown to inhibit various protein tyrosine phosphatases, phosphorylation of the tyrosine kinase receptor by zinc is perhaps the most important critical step of zinc action on human growth.

Thus, it appears that zinc has multiple roles in growth. It is required for IGF-1 generation and phosphorylation of IGF-1 receptor, which are involved in cell division and growth.

ZINC AND GASTROENTERITIS

Gastroenteritis, presenting mostly as diarrhea, is associated with severe zinc deficiency and is frequently seen in developing countries. A pooled analysis of all published and unpublished randomized controlled trials of zinc supplementation in children up to 5 years old with acute or persistent diarrhea found that zinc-supplemented children had a 15% lower probability of continuing diarrhea on a given day.

A Canadian group working in Karachi, Pakistan, reported that mean (SD) longitudinal prevalence of diarrhea among 75 young children aged 6-12 months at high risk of diarrhea-related mortality who received micronutrients with zinc for 2 months was 15% (10%) child-days compared with 26% (20%) child-days in the placebo group.

Among almost 300 children from India with diarrhea resulting in dehydration and hospitalization, stool output was reduced in more than 30% (95% confidence interval [CI] 1-52%) of children receiving zinc treatment compared with children receiving placebo. Duration of illness and proportion of episodes lasting more than 7 days were also substantially reduced.

The mechanism of action of zinc in the management of diarrhea is not completely understood. It is likely to be involved in improving the absorption of fluids from the intestine, helping with clearance of organisms, and supporting regeneration and mucosal integrity, and is likely to have an immunity-related mechanism.

Other roles of zinc can also be discussed, for instance in immunity.

SIDE EFFECTS OF ZINC SUPPLEMENTATION

Till date, there have been no reports of severe adverse reactions from any form of zinc supplementation used in the treatment of diarrhea. A zinc dose of 40 mg has been approved as being safe to use by the US Food and Drug Administration (FDA), and a zinc dosage of more than this can pose certain risks. Too much zinc will probably interfere with the metabolism and absorption of other essential minerals in the body, especially iron, magnesium and copper, reduce the body's immune function and reduce the high-density lipoprotein cholesterol level. Oral zinc sulfate supplements can also cause side effects such as stomach upset, heartburn and nausea.

CONCLUSION

Zinc is an essential element for growth and cell division, fertility, for the immune system, for taste, smell and appetite, for skin, hair and nails, for vision, especially in growing children. Diarrhea is associated with severe zinc deficiency and is frequently seen in developing countries such as India, Bangladesh, Pakistan, etc. The government should start specific programs to educate people about the importance of zinc in growing years of children.

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Clinical Profile of Young Patients with Acute Myocardial Infarction and their SYNTAX Scores

CHAROO PIPLANI*, DEEP CHANDRA PANT†, SHASHI SAXENA‡

ABSTRACT

Objective: To define risk factors, clinical profile and SYNTAX score for young patients (aged 20-40 years) who presented to Shri Ram Murti Smarak (SRMS) Hospital with acute myocardial infarction (MI). **Background:** Myocardial infarction in recent times is known to affect the young as much as it does the old. Various studies like the "INTERHEART", "Role of smoking in global and regional cardiovascular mortality" and "Factors associated with coronary artery disease in young population" over time have proved the significance of multiple risk factors associated with it. **Materials and methods:** The methodology used is a single cross-sectional study with retrospective analysis, with a sample size of 52. Young patients (20-40 years) diagnosed with acute MI who presented to SRMS Hospital in the months of July-December 2018, were included. Data has been analyzed via SPSS version 20, SYNTAX score calculator version 2.28 and Chi-square. **Results:** Of the 52 patients, smoking was associated with the highest number of cases (44.23%) affected with MI and also showed an association with increasing SYNTAX score. The Chi-square value for smoking and SYNTAX score was 4.93, with the p value of 0.041. **Conclusion:** Myocardial infarction, which has become far more common among the younger population group, has been tied to smoking, amongst other factors, playing a major role, in the younger group. Its significant association with the SYNTAX score proves its increasing severity and also its role in creating a huge impact in terms of health in the young adults. Since it is a modifiable risk factor, modification from primary to a primordial level of prevention can be achieved through planned systematic guidelines, which we aimed at concluding from our study.

Keywords: Acute MI, prevent MI, retrospective study, smoking and SYNTAX scores, SYNTAX score, young patients with MI

Coronary artery disease (CAD), in recent times, has become an epidemic in India. The Global Burden of Disease study age-standardized estimates (2010) suggest that around 24.8% of all deaths in India can be attributed to cardiovascular disease (CVD). The age-standardized CVD death rate in India stands at 272 per 1,00,000 population, which is higher than the global average of 235 per 1,00,000 population.[1]

According to PURE (Prospective Urban Rural Epidemiology), a cohort study done in 2014, which had a sample size of 24,000 Indians, the CVD event rate in a largely Indian population was 6.43/1,000 person-years of follow-up compared to 3.99 per 1,000 person-years of follow-up in developed/high-income countries.[1,2] There has been a rising risk of patients presenting with CAD and thus a dire need to prevent that.

In accordance with the data collected by the Report on Medical Certification of Cause of Death, 2015, (Census of India), a total of 11,83,052 medically certified deaths accounted for 22.0% of total registered deaths in respect of 33 States/UTs from which data was available for the report. Diseases of circulatory system accounted for 33.2% of the deaths and amongst the diseases of circulatory system deaths, ischemic heart diseases (IHD) accounted for 26.9% of the deaths.[3]

Furthermore, studies like the INTERHEART study showed that the risk has increased in the younger

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population as well. The effect of potentially modifiable risk factors associated with myocardial infarction (MI) in 52 countries, was assessed and odds ratio (OR) calculated among older (>53 years) versus younger (<53 years) population groups.[4]

In South Asians, apolipoprotein (Apo)B/ApoA1 (OR 3.81) and smoking (OR 2.43) were the important risk factors, as in the rest of the world. However, hypertension (OR 2.89), abdominal obesity (OR 2.43) and diabetes (OR 2.48) had more severe effects in South Asia, whereas psychosocial factors had an OR of 2.15, compared with 2.51 worldwide. It also showed a PAR (population attributable risk) of 14.8% in younger versus 10.45% in older patients.

The first MI attack occurs in 4.4% of Asian women and 9.7% of men at age <40 years, which is 2- to 3.5-fold higher than in the West European population and is third highest of all the regions studied worldwide. These studies carried out in India and other places suggest that Asians in general and Indians in particular are at an increased risk of developing acute MI even at a younger age (<40 years), irrespective of whether they have migrated to other countries or are resident Asians.[4]

The risk factors causing acute MI play a major role in contracting the disease and hence studies in the past have shown their effective role in its causation and prevention. A study on the role of smoking in global and regional cardiovascular mortality was done in the year 2000, and found that an estimated 1.62 million cardiovascular deaths in the world, which is 11% of the overall worldwide cardiovascular deaths, were attributable to smoking.[5]

Another study on the factors associated with CAD in young population, <40 years of age, found that most of the study participants were current smokers (71.6%), and 78.8% had body mass index (BMI) >24 kg/m² and 55.5% usually took high-fat diet. The number of heavy smokers, i.e., those with a smoking history ≥10 years and ≥20 cigarettes per day, were significantly higher in the CAD group compared to the non-CAD group (20.7% vs. 9.3%]).[6]

In a study on CAD in patients younger than 35 years, 200 subjects undergoing coronary angiography were analyzed to find the extent of the disease. Smoking (71%) and history of premature CAD (27%) were found to be the most common risk factors.[7] It is primarily the choice of treatment that determines the disease's mortality rate. Therefore SYNTAX (SYNergy between percutaneous coronary intervention with TAXus and cardiac surgery) score, which is the latest tool in determining the 4-year mortality in accordance with the intervention used, has come into practice in various hospitals. Sixteen studies involving 19,751 participants (8,589 with a low vs. 11,162 with a high SYNTAX score) were included in a meta-analysis. Mortality was significantly higher with a higher SYNTAX score (relative risk [RR] 2.09, 95% confidence interval [CI] 1.78-2.46, p = 0.00001). Cardiac death significantly favored a low SYNTAX score (RR 2.08, 95% CI 1.66-2.61, p = 0.00001). On analyzing patients with ST-segment elevation MI separately, a low SYNTAX score continued to be significantly associated with lower adverse outcomes.[8] It has thus been of prime importance in this study, where the risk and intervention to be used was determined using the SYNTAX score calculator.

AIM

To evaluate the clinical and angiographic findings in young patients presenting with acute MI.

MATERIALS AND METHODS

The methodology used is a single cross-sectional study with retrospective analysis, with a sample size of 52. Young patients (20-40 years) diagnosed with acute MI (World Health Organization [WHO] criteria), who presented to Shri Ram Murti Smarak (SRMS) Hospital in the months of July to December 2018, were included.

Inclusion Criteria

- Patients diagnosed with MI, according to the WHO criteria.[9,10]

  Detection of an increase and/or decline in cardiac biomarker values (preferably cardiac troponin) with at least one value above the 99th percentile of upper reference limit (URL) and at least one of the following:

  - Symptoms of ischemia
  - New or presumably new significant ST-segment T-wave (ST-T) changes or new left bundle branch block (LBBB)
  - Development of pathologic Q waves in ECG
  - Imaging showing new loss of viable myocardium or new regional wall motion abnormality
  - Identification of an intracoronary thrombus on angiography or autopsy.
- Patients in the age group of 20-40 years.

- Patients with <50% reduction in luminal diameter by visual assessment in vessels for SYNTAX scoring.

Exclusion Criteria

- Patients not fulfilling the WHO criteria for MI.
- Patients below 20 years or above 40 years of age.

Clinical profile of young patients with MI has been evaluated for specific risk factors namely positive family history, hypertension, smoking, tobacco use, diabetes mellitus and also angiographic pattern of involvement with SYNTAX scoring.

Analysis has been done in terms of percentages and proportions. Data has been collected from hospital records of the patients who had presented to us in the months of July-December 2018, via a patient proforma, including their name, age, sex, address, admission type, risk factors and symptoms at the time of presentation, investigations, namely ECG, echocardiography, lipid profile, angiography and interventions done. SPSS version 20 was used for analysis. Chi-square was used to find out the association between the risk factors and SYNTAX score (determining the severity of disease).

Percutaneous coronary intervention (PCI) and coronary artery bypass grafting (CABG) are both treatment choices available for revascularization. The location and degree of stenosis are important factors for considering the choice of treatment and thus, there are different degrees of multi-vessel disease and the preferred revascularization strategy may be different for specific lesion complexities. To assess this hypothesis, the angiographic SYNTAX score was introduced, and thus 4-year mortality rates calculated with each intervention.

RESULTS

The study included 52 patients, with male and female patients in the percentages of 92.30% and 7.69%, respectively (Table 1).

Of the 48 males, 2 expired amidst receiving treatment, in the coronary care unit (CCU). The minimum age was 24 and maximum was 40 years. We categorized the patients into two groups of 20-30 and 30-40 years (Table 2).

The risk factor analysis, concluded with hypertension, smoking, tobacco abuse and diabetes mellitus being the major and only determinants from amongst the factors evaluated (Table 3).

Patients were evaluated on the basis of the available data about the risk factors that affected each patient. The collected data revealed that the factors involved in the causation of the disease were modifiable, and hence a part of primary prevention of diseases.

Table 1. Patient Distribution According to Gender

Gender	n	Percentage (%)
Male	48	92.3
Female	4	7.69

Table 2. Patient Distribution According to Age

Age	n	Percentage (%)
20-30 years	7	13.46
30-40 years	45	86.53

Table 3. Evaluation of Risk Factors Affecting the Patients in Percentage

Risk factors	Male n (%)	Female n (%)	Total n (%)
Hypertension	11 (21.15)	3 (5.76)	14 (26.92)
Smoking	23 (44.23)		23 (44.23)
Tobacco chewing	6 (11.53)	1 (1.92)	7 (13.45)
Diabetes mellitus	7 (13.46)	3 (5.76)	10 (19.2)

Smoking had the highest rate of 44.23%, and tobacco chewing the least with the rate of 13.45% amongst others held accountable for causing MI. A total number of 23 patients had a significant history of smoking. The relationship of these factors with the number of patients has been shown in Figure 1.

SYNTAX score is an angiographic grading tool to determine the complexity of CAD. It is used by grading 11 types of lesions by answering questions based on the type of involvement of any number of vessels. We used it from the SYNTAX score calculator website to calculate the severity of disease for the patients included in our study and to find an association with the risk factors.

The Syntax Score Algorithm[11]

- Dominance
- Number of lesions
- Segments involved per lesion, with lesion characteristics
- Total occlusions with subtotal occlusions a. Number of segments; b. Age of total occlusion; c. Blunt stumps; d. Bridging collaterals; e. First segment beyond occlusion visible by antegrade or

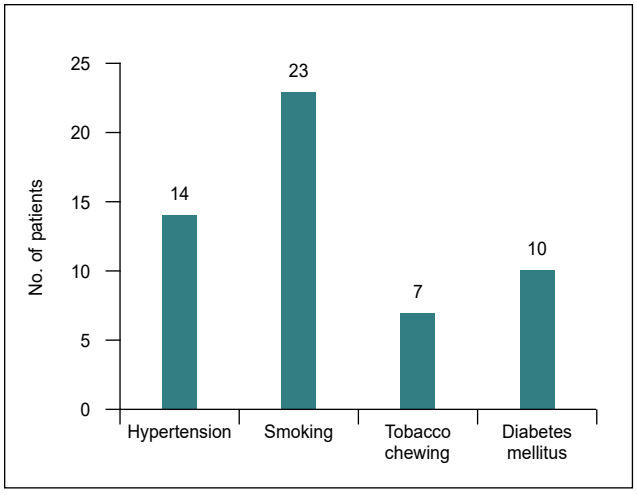

Figure 1. The association of risk factors with the patients of MI.

retrograde flow; f. Side branches involved.

- Trifurcation - number of segments diseased.
- Bifurcation type and angulation.
- Aorto-ostial lesion
- Severe tortuosity
- Lesion length
- Heavy calcifications
- Thrombus
- Diffuse disease, with number of segments.

SYNTAX scoring was possible and done for 50 patients. We categorized them into two groups, with scores of 0-20 and 20-40, from the obtained values in our study.

Chi-square test was used to find the association between the risk factors and SYNTAX score, and the following values were obtained:

- Hypertension: 0.817 (0.656)
- Smoking: 4.93 (0.041)
- Tobacco abuse: 1.361 (0.573)
- Diabetes mellitus: 0.335 (0.620).

It was noted that there was an association between smoking and patients with increased scores, hence the severity of disease, which was significant with the p value of 0.041 (Table 4).

It was also seen that the occurrence of disease increased with age, with the maximum number of patients lying in the age group of 35-40 years (Fig. 2).

Patients presenting to us came with various preceding symptoms, chest pain recording the highest number, followed by its radiation and nausea and vomiting being the least common. A detailed account of these symptoms in the patients is given in Table 5.

Table 4. Cross Tabulation of SYNTAX Score and Risk Factors

SYNTAX score ⇒ / Risk factors ⇓	Score: 0-20 (43)	Score: 20-40 (7)	Total	Chi-square	P value
Hypertension	13	1	14	0.817	0.656
Smoking	17	6	23	4.93	0.041
Tobacco abuse	7	0	7	1.361	0.573
Diabetes mellitus	8	2	10	0.335	0.620

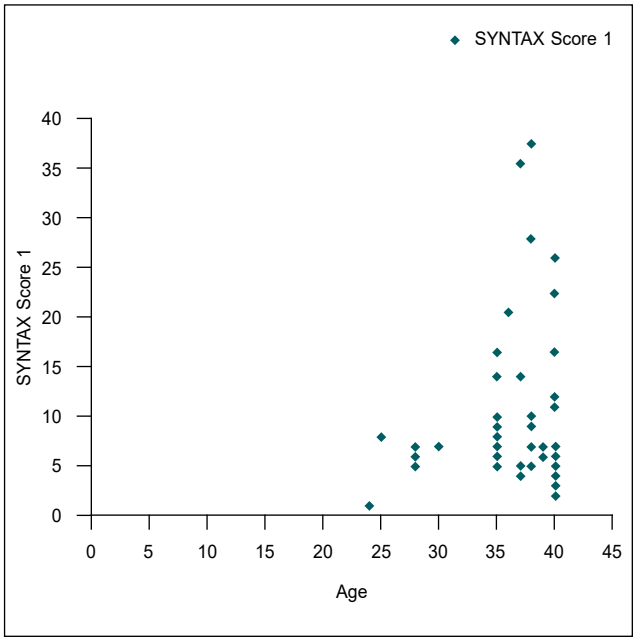

Figure 2. Association of occurrence of disease with age.

The different presentations of MI were seen as:

- Anterior: 44.2% (n = 23)
- Inferior: 19.2% (n = 10)
- Anteroseptal: 11.5% (n = 6)
- Anterolateral: 7.69% (n = 4)
- Inferolateral: 7.69% (n = 4)
- Septal: 3.84% (n = 2)
- Posterior: 1.92% (n = 1)
- Inferoposterior: 1.92% (n = 1)
- Lateral: 1.92% (n = 1)

Amongst the various investigations, lipid profile could be done for 41 patients within 24 hours of admission with raised values for 8 patients:

Table 5. Preceding Symptoms in Study Participants

Symptoms	Male n (%)	Female n (%)	Total n (%)
Chest pain	46 (88.4)	3 (5.76)	49 (94.23)
Radiation of pain	41 (78.84)	2 (3.84)	43 (82.69)
Chest tightness	23 (44.23)	1 (1.92)	24 (46.15)
Sweating	29 (55.7)		29 (55.7)
Nausea/vomiting	6 (11.5)	1 (1.92)	7 (13.4)
Breathlessness	8 (15.38)	3 (5.76)	11 (21.15)
Anxiety	27 (51.9)	1 (1.92)	28 (53.84)

- Raised triglyceride with low high-density lipoprotein (HDL): 9.6% (n = 5)
- Raised triglyceride only: 3.84% (n = 2)
- Raised triglyceride and low-density lipoprotein (LDL): 1.92% (n = 1)

Family history was noted as positive for MI for a total of 6 patients.

Severity of SYNTAX score has been classified on the basis of scores: <22 (low risk); 23-32 (moderate risk) and >33 (high risk).[12]

The algorithm for calculation of SYNTAX score has been attached as Annexure A.

- Low risk = 84.61% (n = 44)
- Moderate risk = 7.69% (n = 4)
- High risk = 3.84% (n = 2)
- Expired mid treatment = 3.84% (n = 2)

DISCUSSION AND CONCLUSION

Myocardial infarction has become more common among the younger population. Smoking plays a major role in the younger group that we studied. Furthermore, its significant association (p value) with the SYNTAX score as per our study only proves its prime and sole importance. We know for a fact that it is a modifiable factor that can be overmatched at the primary level of prevention of disease. Young adults indulge themselves into activities like cigarette and bidi (in rural India) smoking from as early as their teens, while they are in school. So, inculcating the risk awareness plan as a part of primary institutional education, in the form of animated clips, camps or awareness campaigns regularly, understandable at their level, can further modify and prevent its occurrence, thus making it a primordial level of prevention, which was aimed at in our study to bring about changes or facts to our attention that will help abolish the disease for good or prevent its occurrence from this risk factor.

The male: female ratio also had a vast difference in our study possibly due to the hormone estrogen, acting as a protective factor in the younger females, and partly due to poor economic status and lack of awareness, in the rural Indian setting, that may have influenced the female intake of patients being lesser than that of males.

The symptomatology - chest pain - is an alarming symptom that must be promptly attended to and diagnosed as early as possible (minutes mean muscle), via clinical and biochemical examinations, as it already is in most clinical settings. Lastly SYNTAX score, besides forming a significant association with the risk factors, has been seen as an effective calculator showing the 4-year mortality and choice of intervention that must ideally be used to treat the patient, thereby aiding in decreased mortality rates in the future for them.

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Annexure A[11]

Segment No.	Segment name	Right dominance	Left dominance
1	RCA proximal	1	0
2	RCA mid	1	0
3	RCA distal	1	0
4	Posterior descending artery	1	NA
16	Posterolateral branch from RCA	0.5	NA
16a	Posterolateral branch from RCA	0.5	NA
16b	Posterolateral branch from RCA	0.5	NA
16c	Posterolateral branch from RCA	0.5	NA
5	Left main	5	6
6	LAD proximal	3.5	3.5
7	LAD mid	2.5	2.5
8	LAD apical	1	1
9	First diagonal	1	1
9[a]	First diagonal[a]	1	1
10	Second diagonal	0.5	0.5
10[a]	Second diagonal[a]	0.5	0.5
11	Proximal circumflex artery	1.5	2.5
12	Intermediate/anterolateral artery	1	1
12[a]	Obtuse marginal[a]	1	1
12[b]	Obtuse marginal[b]	1	1
13	Distal circumflex artery	0.5	1.5
14	Left posterolateral	0.5	1
14[a]	Left posterolateral[a]	0.5	1
14[b]	Left posterolateral[b]	0.5	1
15	Posterior descending	NA	1

Lesions adverse characteristic scoring[11]

Diameter reduction*

- Total occlusion x5
- Significant lesion (50-99%) x2

Total occlusion (TO)

- Age >3 months or not known +1
- Blunt stump +1
- Bridging +1

➲ First segment visible beyond TO	+1/per nonvisible segment
➲ Side branch (SB) - Yes, SB <1.5 mm**	+1
Yes, both SB < & ≥1.5 mm	+1
Trifurcations	
➲ 1 diseased segment	+3
➲ 2 diseased segments	+4
➲ 3 diseased segments	+5
➲ 4 diseased segments	+6
Bifurcations	
Type A, B, C	+1
Type D, E, F, G	+2
Angulation <70°	+1
Aorto-ostial stenosis	+1
Severe tortuosity	+2
Length >20 mm	+1
Heavy calcification	+2
Thrombus	+1
"Diffuse disease"/small vessels	+1 per segment number

x = Multiplication; + = Addition.

RCA = Right coronary artery; LAD = Left anterior descending.

*In the SYNTAX algorithm there is no question for % luminal diameter reduction. The lesions are considered as significant (50-99% luminal diameter reduction) or occlusive.

**If all the side branches are 1.5 mm in diameter, no points are added as the lesion is considered as a bifurcation and will be scored as such.

■■■■

The Effect of a Multivitamin and Mineral Supplement on Immune Function in Healthy Older Adults

Older adults are at increased risk for vitamin and mineral deficiencies that contribute to age-related immune system decline.

A new study published in *Nutrients* aimed to test the hypothesis that taking a multivitamin and mineral supplement (MVM) could improve immune function in individuals at the age of 55 years and older.

In this double-blinded, randomized, controlled trial provided healthy older adults with either an MVM supplement formulated to improve immune function or an identical, inactive placebo control – to be taken daily for 12 weeks. The patients' blood mineral and vitamin status – vitamin C, zinc and vitamin D; immune function – whole blood bacterial killing activity, neutrophil phagocytic activity and reactive oxygen species production; immune status – salivary IgA and plasma cytokine/chemokine levels and self-reported health status were measured—prior to and after treatment.

The findings indicated that MVM supplementation improved vitamin C and zinc status in blood, as well as the self-reported health-status, without altering measures of immune function or status or vitamin D levels. The findings suggested that healthy older adults may benefit from MVM supplementation.

It was concluded that further development of functional assays and larger study populations should improve detection of specific changes in immune function after zinc supplementation in healthy older adults.

Source: Fantacone ML, Lowry MB, Uesugi SL, et al. Nutrients. 2020;12(8):E2447.

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To Study the Prevalence of Metabolic Syndrome and Dyslipidemia in Patients of Xanthelasma Palpebrarum at a Tertiary Care Hospital

SWATI GONDANE*, ASHOK MEHERDA†, RAJKUMAR KOTHIWALA‡

ABSTRACT

Background: Xanthelasma palpebrarum (XP) are yellow plaques that occur most commonly near the inner canthus of the eyelid, more often on the upper lid than the lower lid and are often associated with dyslipidemia, metabolic syndrome, cardiovascular disease, diabetes, obesity, etc. **Aim:** This study was planned to address the issue of prevalence of dyslipidemia and metabolic syndrome in xanthelasma patients attending dermatology clinic at a tertiary care hospital, Ajmer. **Material and methods:** A total of 73 patients were detected to be having xanthelasma and constituted the study group. The control group constituted 73 apparently normal individuals. Each patient underwent detailed history and examination. Body mass index (BMI), waist circumference, arterial blood pressures, fasting plasma glucose (FPG), serum lipids and liver enzyme levels were estimated in cases and controls. **Results:** The most prevalent age group was 40-50 years. Females outnumbered males. Dyslipidemia was present in 63% and metabolic syndrome in 45.2% of cases. The mean levels of FPG, BMI, waist circumference in XP patients were significantly higher in patients than those in controls. **Conclusions:** A significant number of cases of XP are found to be associated with metabolic syndrome, central obesity, hypertension, diabetes mellitus and dyslipidemia which are the major risk factors for coronary artery diseases. Efforts should be made to rule out the same in xanthelasma subjects.

Keywords: Xanthelasma, dyslipidemia, metabolic syndrome

Xanthelasma palpebrarum (XP) (Greek; *xanthos*: yellow and *elasma*: beaten metal plate) are yellow plaques that occur commonly near the inner canthus of the eyelid, more often on the upper lid.[1] Xanthelasma can be soft, semisolid or calcareous, and are frequently symmetrical with all four-eyelid involvement. They have a tendency to progress, coalesce and become permanent. Xanthelasma represent areas of macrophage-containing lipids, primarily cholesterol esters, but the exact pathogenesis is not known.[2] Xanthelasma are composed of xanthoma cells which are foamy histiocytes laden with intracellular fat deposits primarily within the upper reticular dermis. Most studies have found increased concentrations of plasma total cholesterol or low-density lipoprotein (LDL) cholesterol in people with xanthelasma. It has been known to be associated with atherosclerosis, coronary artery disease (CAD), insulin resistance, diabetes mellitus (DM), hypertension, stroke, dyslipidemia, obesity and hyperuricemia. However, it is still controversial whether such lesions are a marker for cardiovascular or metabolic disease or not.

A study was planned to address the issue of prevalence of metabolic syndrome and dyslipidemia in xanthelasma patients attending dermatology clinic at our center.

MATERIAL AND METHODS

This study was conducted in the Dept. of Dermatology at JLN Medical College, Ajmer, Rajasthan. Seventy-three clinically diagnosed cases of XP were selected after informed consent and these constituted the study group. Control group was age- and gender-matched apparently healthy participants with no xanthelasma, randomly selected from the outpatient clinic.

Exclusion criteria were patients taking any drugs that could alter lipid level or blood glucose level, patient having concomitant disorder(s) that could affect the

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outcome of the study. Each patient underwent detailed history and physical examination including height, weight, waist and hip circumference. Body mass index (BMI) was calculated for the participants in both groups and obesity was defined by BMI 30 or greater.

All blood pressure (BP) measurements were taken with standard calibrated mercury manometers in the right arm of each individual in a sitting position after a rest of 5 minutes. Fasting blood samples were collected after 14-hour fasting. All cases underwent lipid profile study (total cholesterol [TC], LDL cholesterol, high-density lipoprotein [HDL] cholesterol, very low-density lipoprotein [VLDL], triglycerides [TGs]) on empty stomach.

Dyslipidemia: Abnormal lipid levels were diagnosed according to the National Cholesterol Education Program-Adult Treatment Panel III (NCEP-ATP III) guidelines.

Metabolic syndrome: According to the third report of the NCEP-ATP III, adults to be diagnosed with metabolic syndrome must have three or more of the following:

- Waist circumference >102 cm (40.2 in) in men and >88 cm (35.6 in) in women
- Serum TGs ≥150 mg/dL
- BP ≥130/85 mmHg
- HDL cholesterol <40 mg/dL in men and <50 mg/dL in women
- Fasting plasma glucose (FPG) >6.1 mmol/L (≥100 mg/dL).

Data were statistically described in terms of mean (standard deviation), frequency (number of cases) and percentages when appropriate. Comparison of quantitative variables between the study groups was carried out using the Student's *t*-test and Chi-squared test, respectively. Statistical analysis was carried out using graphpad software.

RESULTS

The total number of cases of xanthelasma and controls was 73. The youngest case with XP was 30 years of age, while the eldest was 73 years old, mean age of the cases being 51.18 and that of controls 52.01 with a 't' value of 0.4829 and p value of 0.6299 making the two groups statistically comparable. Prevalence was the highest in the age group of 40-50 years (33%). Prevalence was higher in females (82.2%) as compared to males (17.8%). Most of the cases (93.15%) were Hindus, while 6.85% were Muslims. While xanthelasma was found mostly bilaterally (56 cases; 76.72%), unilateral presentation was found in 17 cases (23.28%). In 9 cases (12.32%), it was present on all four eyelids. Family history of XP was obtained in 8 cases (10.95%) in our study.

TC levels were increased in 46 cases (63.01%) as compared to 20 controls (27.4%). Similarly, LDL cholesterol and TG levels were also increased in 52 cases (71.2%) as compared to 29 controls (39.72%) and in 29 cases (39.7%) as compared to 17 (23.3%) controls, respectively. HDL levels were decreased in 34 cases (46.6%) as compared to 22 controls (30.1%). VLDL cholesterol was increased in 15 cases (20.5%) and 11 controls (15%). Mean values of TC, LDL cholesterol and TG levels were increased compared to control group with significant p value. Mean value of HDL cholesterol was found to be decreased compared to control group with significant p value; however, p value was not found to be significant in mean value of VLDL cholesterol compared to controls (Table 1).

Nearly, 18 (24.66%) patients and 8 (11%) controls were diagnosed with DM according to the American Diabetes Association (ADA) criteria and this difference was statistically significant (p = 0.0305).

Table 1. Relationship Between Various Cholesterol Fractions and XP in Cases and Controls

	Mean	SD	t value	P value*
TC				
Cases	212.6	(34.8)	4.9843	<0.0001 Highly significant
Control	181.8	(39.6)		
LDL				
Cases	137.3	(23.52)	3.4434	P = 0.0008 Highly significant
Control	124.3	(21.92)		
HDL				
Cases	41.33	(7.87)	2.288	P = 0.0236 Significant
Control	44.35	(8.09)		
TG				
Cases	152.29	(70.09)	2.1352	P = 0.0344 Significant
Control	132.27	(38.74)		
VLDL				
Cases	30.10	(15.89)	0.9445	P = 0.3465 Not significant
Control	27.8	(12.18)		

XP = Xanthelasma palpebrarum; TC = Total cholesterol; LDL = Low-density lipoprotein; HDL = High-density lipoprotein; TG = Triglyceride; VLDL = Very low-density lipoprotein; SD = Standard deviation.

*P < 0.05 is considered to be statistically significant.

Table 2. Comparison Between Various Metabolic Syndrome Components in XP Patients and Controls

	No. of the patients		P value*
WC			
Cases	↑ 48 (65.8%)	N 25 (34.2%)	P = 0.0298 Significant
Control	↑ 35 (48%)	N 38 (52%)	
BP			
Cases	↑ 22 (30%)	N 51 (70%)	P = 1.245 Not significant
Control	↑ 14 (19.2%)	N 59 (80.8%)	
HDL			
Cases	↓44 (60.3%)	N 29 (39.7%)	P = 0.0314 Significant
Control	↓31 (42.5%)	N 42 (57.5%)	
TG			
Cases	↑29 (39.7%)	N 44 (60.3%)	P = 0.0325 Significant
Control	↑17 (23.3%)	N 56 (76.7%)	
MS			
Cases	P 33 (45.2%)	A 40 (54.8%)	P = 0.0002 Highly significant
Control	P 12 (16.4%)	A 61 (83.6%)	

XP = Xanthelasma palpebrarum; WC = Waist circumference; BP = Blood pressure; HDL = High-density lipoprotein; TG = Triglyceride; MS = Metabolic syndrome; ↑ = Increased; ↓ = Decreased; N = Normal; P = Disease present; A = Disease absent.

*P < 0.05 is considered to be statistically significant calculated from Chi-squared test.

Metabolic syndrome was present in 45.2% (33 cases) in XP patients as compared to 16.4% (12 cases) in control group with significant p value (p = 0.0002). Individual components of metabolic syndrome like hypertriglyceridemia, decreased HDL cholesterol, impaired FPG and waist circumference were also more prevalent in cases than in controls (Table 2).

However, systolic and diastolic BP were noted to be higher among cases (22 cases, 30%) as compared to controls (14 cases, 19.2%) but p value was not found to be statistically significant (p = 1.245). Mean value for BMI in case group (27.71) was higher than control group (26.50) with significant p value (p = 0.0268).

DISCUSSION

Xanthelasma is fairly prevalent in our population. However, people tend to complain only for esthetic reasons. Most of our cases were not aware of the significance of these deposits. Age distribution was wide ranging from 21 to 73 years. We found the peak incidence between 40 and 60 years. This was similar as that reported by Gangopadadhya et al[3] and Jain et al[2] in their studies from Delhi. They found the majority of patients in the age group of 31-50 years. XP was found more in females (82.2%) as compared to males (17.8%) in our study. This was in concurrence with the study done by Jain et al, Gangopadadhya et al, Epstein et al and Pedace et al.[2-5] But Chhetri et al[6] showed a male preponderance in his study. Jain et al, Chhetri et al and Reddy et al found a positive family history in 12.1%, 8.9% and 9.8% patients, respectively.[2,6,7] Family history of XP noted in our cases was 10.95%, similar to 10% cases with positive family history found by Vacca et al.[8]

Jain et al reported that 91% of patients had multiple lesions and 72.7% had both lids involvement. Two or more eyelids involvement was observed in 87.9% of the cases.[2] Chhetri et al reported bilateral lesions in 39% cases, two eyelids involvement in 53.2% cases and one eyelid involvement in 7.8% cases.[6] Ribera et al reported that 11.3% patients had only one eyelid involvement, 42.6% in two eyelids, 12.2% in three eyelids and 33.9% in four eyelids.[9] In our study, 56 cases (76.72%) had bilateral lesions and 17 cases (23.28%) had unilateral lesions. Single lesions were present in 14 cases (19.18%) and multiple lesions were present in 59 cases (80.82%).

We found associations with hypertension, dyslipidemia, metabolic syndrome and diabetes in a sizeable percentage of our patients. Increased TC value in xanthelasma patients have been observed by Gangopadadhya et al, Epstein et al, Pedace et al and Kahán et al.[3-5,10] We also found similar results with TC levels increased in 46 cases (63%) as compared to 20 controls (27.4%) with p < 0.0001, making it highly significant. Increased LDL cholesterol levels have been observed by various authors.[3,9,11-13]

The study done by Vermeer et al[14] found it to be normal. Our study showed increased LDL cholesterol levels in 52 cases (71.2%) as compared to 29 controls (39.72%), which was more significant in comparison to other studies and was statistically significant with p value of 0.001. Gangopadadhya et al,[3] Bates et al[15] and Ribera et al[9] observed a significant decrease in HDL cholesterol levels. Similar results were shown in our study, which observed a decrease in HDL cholesterol in 34 cases (46.6%) as compared to 22 control (30.1%) with a significant p value of 0.0411.

We found TGs were increased in 29 cases (39.7%) and 17 controls (23.3%) with a significant p value of 0.0325 as observed by many authors,[2,3,6,10,16] although there

were no comparisons with controls by some authors. These findings were not similar to study done by Ribera et al in which 5.21% cases and 6.66% controls showed hypertriglyceridemia.[9] Watanabe et al reported that VLDL levels were significantly above the control levels ($p = 0.001$) in cases.[11] Sharma et al and Jain et al observed a significant increase in VLDL levels in patients with xanthelasma as compared to controls ($p < 0.01$, $p = 0.001$).[2,17] In our study, VLDL cholesterol was increased in 15 cases (20.5%) and 11 controls (15%) but difference was not found to be statistically significant ($p = 0.3869$).

Jain et al[2] found that 42.4% of patients had associated systemic diseases like hypertension, CAD, DM and cholelithiasis. Chhetri[6] and Gangopadadhya[3] reported cardiovascular disease (CVD) and hypertension in patients of XP in their studies. From western countries incidence of DM associated with XP was reported to be 6-34.2%.[8,9] Clinical study done by Dey et al had observed prevalence of DM as 18.03% in XP.[18] In our study, 18 cases (24.66%) had DM as compared to 8 (11%) controls with significant p value ($p = 0.0305$). Various studies have observed that subjects with DM, hypertension, metabolic syndrome and dyslipidemia have increased risk of CVDs.[19-21]

We found metabolic syndrome was present in 45.2% (33 cases) in XP patients as compared to 16.4% (12 cases) in control group with significant p value ($p = 0.0002$). Individual components of metabolic syndrome like hypertriglyceridemia, decreased HDL cholesterol, impaired FPG, BMI and waist circumference were also observed more prevalent in cases than in controls.

Whether or not xanthelasma alone can predict risk of CAD is still not clear, although studies have shown that it can. Christoffersen et al[22] reported that xanthelasma can predict the risk of myocardial infarction, ischemic heart disease, severe atherosclerosis and death in the general population, independently of the well-known cardiovascular risk factors.[18]

At the end of this study, it was observed that there is a significant elevation in lipid profile in xanthelasma patients as compared to controls, thereby making lipid profile study mandatory for all patients. We also found significant association of DM and metabolic syndrome in xanthelasma patients as compared to controls. The presence of xanthelasma merits identification and treatment in order to prevent metabolic syndrome, which is gaining epidemic proportions in our country.

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■■■■

COVID-19 Cases Increase in Children in US, Deaths Remain Low

Children accounted for 9.3% of all COVID-19 cases in the US as of August 20, representing a rise from 9.1% the previous week, but only 0.06% of all US deaths reported, suggests a report from the American Academy of Pediatrics (AAP) and the Children's Hospital Association (CHA).

The cumulative number of pediatric cases reported till that date stood at 4,42,785, representing 9.3% of the total COVID-19 case load of over 4.76 million among all ages. There have been 92 pediatric deaths, which amounts to 0.06% of the 1,54,279 deaths reported among all ages, stated the AAP and the CHA said in a recent update. Hospitalizations among children are also low, representing 1.7% (4,062) of the cumulative total of 2,34,810 admissions among all ages as of August 20, as per data obtained from 21 states and New York City… (*Medscape*)

WHO African Region Certified as Wild Polio-free

The WHO African Region has been certified as wild polio-free by the Africa Regional Certification Commission, after 4 years without a case.

Five of the six WHO regions, having more than 90% of the world's population, are now declared free of the wild poliovirus. The only two countries where wild poliovirus transmission is still prevalent include Pakistan and Afghanistan. The Global Polio Eradication Initiative (GPEI) congratulated the governments of the 47 countries in the WHO African Region for achieving the milestone. WHO Director-General, Dr Tedros Adhanom Ghebreyesus said that eradication of the wild poliovirus in Africa is among the greatest public health achievements of the present time and inspires all to eradicate polio on a global level… (*WHO*)

FDA Authorizes First Diagnostic Test for COVID-19 that Enables Reading Results Directly from Testing Card

The US FDA has issued an emergency use authorization for the first COVID-19 antigen test that enables reading the results directly from the testing card, somewhat similar to some pregnancy tests.

This is a fast and efficient test for healthcare providers and patients and does not require an analyzer. For the test, a healthcare provider swabs the patient's nose and is then required to whirl the sample on a test card with a reagent added. After 15 minutes, the healthcare provider can read the results directly from the testing card, where appearance of one line indicates a negative result while two lines suggest a positive result… (*FDA*)

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Study of hs-CRP in HIV Patients and Its Correlation with CD4 Count

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ABSTRACT

Objectives: The ever-growing prevalence of human immunodeficiency virus (HIV) infection in developing nations had long called for the need to optimize the health resources spent over HIV patients. In such a scenario, monitoring of disease progression in HIV patients with CD4 estimation biennially is a luxury only few countries can afford. In our study, we evaluated the potential role of high-sensitivity C-reactive protein (hs-CRP) as a cheaper alternative for CD4 estimation by assessing the correlation that exists between the two parameters. **Study design:** This was an open-labeled randomized, cross-sectional study. We measured hs-CRP and CD4 counts in 142 HIV patients (16 children and 126 adults) and evaluated the correlation between the two parameters with regards to different patient characteristics. **Results:** We found a statistically significant negative correlation between the two variables ($p < 0.001$). This strong negative correlation persisted in different subgroups of the study population formed with respect to age, sex, antiretroviral therapy (ART) status, different ART regimen, hemoglobin status, body mass index, duration and stage of the disease. Only in underweight patients, the negative correlation between hs-CRP and CD4 counts did not reach statistical significance ($p > 0.05$). **Conclusion:** hs-CRP does hold the exciting possibility of being the cheaper alternative marker of disease progression in HIV patients pending further studies.

Keywords: Human immunodeficiency virus, high-sensitivity C-reactive protein, cluster of differentiation, immunoturbidimetry

Despite being the burning topic of clinical research for more than three decades, the cure for human immunodeficiency virus-acquired immune deficiency syndrome (HIV-AIDS) remains elusive till date. Since, the introduction of first antiretroviral drug in late 1990, more than 25 licensed antiretroviral drugs are currently available for the management of HIV infection. These drugs have transformed HIV from a progressive disease with a fatal outcome into a chronic manageable disease.

With improved antiretroviral therapy (ART) regimens and widespread availability of ART drugs, more and more patients are now entering into chronic disease phase and are having improved mortality rates. This has resulted in overall increase in prevalence of HIV infection even though the incidence of new cases with each passing year is gradually coming down. With widespread increase in prevalence of HIV infection and the growing emphasis on improved healthcare for HIV-infected patients, the overall cost of management of HIV patients has placed a huge economic burden on health infrastructure of every nation, more so for developing countries like India.

This scenario of growing patient population along with limited health resources calls for optimum utilization of available resources for maximizing benefits. In this situation, periodic measurement of CD4 counts for monitoring HIV disease progression is a luxury which many countries can no longer afford, even though CD4 count remains the gold standard tool for monitoring HIV disease progression. This is considered by many experts as a wasteful expenditure in resource poor settings especially for patients with disease stage 1 or 2 on combination ART regimen for at least 2 years with either persistently stable CD4 counts or HIV RNA levels below 50 copies/μL.[1] This has resulted in a long-term demand for an alternate marker for monitoring HIV disease progression that could show reliable correlation with CD4 counts and at the same

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time cheaper to perform. All the HIV disease-specific markers earlier proposed were costly and least effective when compared to CD4 monitoring. There were few non-HIV-specific markers of inflammation, which have been proposed as a potential replacement marker of CD4 count estimation.

These include:

- Interleukin (IL)-6
- Soluble CD14
- D-dimer
- High-sensitivity C-reactive protein (hs-CRP).

Among the four, measuring IL-6 and soluble CD14 is a costly venture when compared to the cost of measuring CD4. This leaves us with two options. Among the two, earlier studies with D-dimer were highly disappointing. While studies showing direct correlation of hs-CRP with CD4 counts were lacking. This prompted us to work on this topic. Our primary objective was to estimate the levels of serum hs-CRP in HIV-infected patients and to find out whether any correlation exists between serum hs-CRP levels and CD4 counts of HIV patients. Our secondary objective was to evaluate whether this correlation holds good in different subgroups.

MATERIAL AND METHODS

Participants

We carried out this study within the framework of the National AIDS Control Programme (NACP) with diagnosis and treatment of HIV patients conducted in accordance with recommended procedures. Patients detected to be HIV positive confirmed by western blot attending ART center, JN Medical College and Hospital, AMU, Aligarh, were taken up for the study. The present study included all patients who attended our ART center from January 2014 up to February 2015. Patients who had confounding factors that could potentially influence hs-CRP levels were excluded from the study. The exclusion criterion included:

- Any hospitalized patients or those with history of any acute illness in preceding 2 weeks.
- Patients with World Health Organization (WHO) Stage 4 disease.
- Patients with liver dysfunction.
  - Deranged liver function tests, i.e., total bilirubin >1.5 mg/dL and/or liver enzyme levels ≥3 times of upper normal limit
  - Concomitant viral hepatitis B or C (hepatitis B surface antigen/anti-HCV antibody).
- Body mass index (BMI) ≥25 kg/m^2 (Asian cut-off for obesity).
- Deranged lipid profile: Triglyceride >150; low-density lipoprotein (LDL) cholesterol >100 mg/dL.
- History of cardiovascular disease or any long-term medical illness, which requires medication for more than 3 months apart from HIV infection.
- History of smoking (current or past).

Study Design

This study was an open-labeled, randomized, cross-sectional study. Patients attending our ART center were seen on a first come first serve basis. More than 400 patients attended the ART center during the study period. It included patients who come for 6-monthly laboratory check-up, monthly drugs collection and those newly diagnosed. Each person had an ART number and a patient card. They then waited until their number was called to be seen by the clinician. When the patient arrived, the examining clinician referred him/her to the researcher. The researcher queried their interest in participating in this study. If interested, the researcher reviewed eligibility criteria and explained the purpose of the study, benefits and risks as part of the informed consent. Adequate time was given for the participant to consider participation. A written informed consent was obtained from all individuals who agreed to participate. A study ID number was then allocated. Our study included a total of 142 HIV patients of which 72 were male and 70 were female.

A standard data abstraction tool relating to clinical history was developed and used to abstract required information from the patients files/charts and HIV/AIDS treatment and monitoring database. The following data were recorded: duration and kind of ART, CD4 cell count, complete blood cell (CBC) count and blood chemistries (viz., creatinine, aspartate aminotransferase [AST] and alanine aminotransferase [ALT]), demographic data such as age and sex, duration and stage of HIV infection according to WHO criteria.[2] HIV and ART duration were calculated from the date confirmed HIV positive and date started ART, respectively to the date when blood sample for hs-CRP analysis was taken and age was calculated from the date of birth to the date when blood taken for hs-CRP.

Sample Collection

Under aseptic techniques, we performed routine venous puncture. Using a serum separator tube (SST; Becton Dickinson, Franklin Lakes, NJ, USA), 7 mL

nonfasting whole blood was drawn and left to clot for about 30 minutes, followed by centrifugation for 12-15 minutes.

Complete blood cell count

CBC counts were done using Sysmex KX-21 (Sysmex Corporation; Kobe Japan). The machine automatically dilutes a whole blood sample, lyses, counts and gives a printout result of absolute numbers of leukocytes (expressed as number of cells × [10^9] per liter), erythrocytes (number of cells × [10^{12}] per liter), platelets (number of cells × [10^9] per liter), lymphocytes (number of cells × [10^9] per liter), mononuclear cells (number of cells × [10^9] per liter), granulocytes (number of cells × [10^9] per liter) and hemoglobin (grams per deciliter). The quality and accuracy of the technique and the machine was assessed every 6 months.

Renal function tests

- **Blood urea:** This was performed by Nessler's method.
- **Serum creatinine:** This was estimated by Jaffe's method.

Liver function tests

- **Total serum bilirubin:** Estimated by Van den Bergh method of calorimetry.
- **AST/ALT:** Serum AST and ALT were estimated by simplified calorimetric test at 505 nm.
- **Alkaline phosphatase (ALP):** Estimated calorimetrically by the test described by EJ King.

CD4 T cell counts analysis

Cluster differential cells (CD4 T cells) were analyzed using a FACSCount Flow cytometer (Becton Dickinson Immunocytometry Systems, San Jose, Calif). In brief, 50 μL of whole blood was mixed and incubated at room temperature for 20 minutes with 20 μL of a test solution. Red blood cells (RBCs) were then lysed by adding 450 μL of fluorescence-activated cell sorter lysing solution. The tubes were incubated at room temperature for 10 minutes, and then analyzed with the FACS Count's CellQuest software (Becton Dickinson Immunocytometry Systems) within 6 hours. By using quality control (Multi check; Becton Dickinson Immunocytometry Systems), the accuracy of the technique was assessed every 6 months.

Measurement of hs-CRP

In our study, hs-CRP was measured by immunoturbidimetry method. It works on the principal of light scattering by interaction with particles in solution. Turbidimetry is an analytical technique that uses light scattering principle to measure the concentration of particle in the solution. The photometric signal is generated by a decrease in light intensity as a direct consequence of increasing turbidity in the reaction well. The reaction occurring in the well is the classical antigen-antibody reaction, hence the name immunoturbidimetry. The photometric signal is then detected by a photometer. In our study, serum was separated from patient's blood samples and stored in separate serotops. The samples were processed in batches with the storage time of each sample not exceeding more than 2 weeks. The kit used in our test was Agape hs-CRP kit and the analysis was performed using a BIOLIS-242 auto analyzer. The hs-CRP levels were measured in mg/L units.

Data Management

The principal investigator abstracted and filled the information obtained from the patient's file to the abstraction forms. Immediately following completion of abstraction form, the researcher double checked the instruments for completeness and consistency of answers. Completed abstraction forms were then coded by numbers and entered in Microsoft Excel sheet version 2010. Cross-checking and data cleaning was done. During data cleaning and cross-checking missing information were obtained by going back to the abstraction form, HIV treatment and monitoring database and when necessary reviewing the patients on the next visit to the clinics. The data were then transferred to SPSS version 21 software for analysis.

Statistical Analysis

All analyses were performed with SPSS software for Windows, version 21 (SPSS Inc., IBM, Version 21.0, USA).

Statistical tests applied

- Spearman's bivariate correlation coefficient test.
- Independent sample *t*-test.
- One way ANOVA with post-hoc analysis done using Tukey's HSD method, wherever needed.

In our study, we considered patients up to 14 years as pediatric population. No attempt was made from our side to classify patient's stage of disease. The WHO clinical stage allotted to each patient from the ART center of our institute at the time of sample collection was used as such in our study.[2,3] WHO BMI staging for South-East Asian population was used to exclude obese patients with BMI ≥25 kg/m^2.[4] WHO classification was used to classify patient's hemoglobin values.[5] Patients

taking ART in our study were following one of the three NACO's (National AIDS Control Organization) ART regimen - Regimen 1, 2 or 2a.[6] The American Heart Association (AHA) risk grading of hs-CRP used by Shikuma et al[7] was used in our study to classify patients based on hs-CRP values into 4 groups (Low - ≤1 mg/L, Average - 1.1-3 mg/L, High - 3.1-10 mg/L and Outliers - ≥10.1 mg/L). We also made 3 groups based on CD4 counts (≤200, 201 up to 500 and >500).

RESULTS

In our study, 200 HIV patients were chosen randomly. After applying exclusion criteria, 142 patients were selected for measuring hs-CRP. Out of 142, 16 (11%) patients belonged to pediatric age group (≤14 years) and 126 (89%) patients were adults. Among 126 adults, there were 61 (48%) males and 65 (52%) females. Regarding ART status, 21 (15%) patients were not taking ART, which included 12 males and 9 females. Rest of the patients (121) were on ART. In our study, 36 (25%) patients had Stage 1 disease, which included 10 males and 26 females. Seventy-four (52%) patients had Stage 2 disease out of which 43 were males and 31 were females. There were 32 (23%) Stage 3 patients in our study, which included 19 males and 13 females. The distribution of study population is depicted in Figure 1.

The mean CD4 count of the study population was 361.8 ± 183. The CD4 count ranged from 27 to 1,402 in our study. Thirty-one patients had CD4 count ≤200 cells/mm^3 and another 31 had CD4 count >500 cells/mm^3. While 80 patients had CD4 count in the 200-500 cells/mm^3 range.

The hs-CRP values in the study population ranged from 0.10 to 169.70 mg/L with a mean of 7.9239 ± 23.55 mg/L. Fifty-one patients had low (≤1), 49 had average (1.1 up to 3), 25 had high (3.1 up to 10) hs-CRP values. Seventeen patients had hs-CRP in the outliers (>10) range.

Distribution of study population based on hs-CRP and other baseline characteristics is as shown in Table 1. Outliers were excluded from all statistical analysis. Subgroups with less than 10 entries (viz., moderate and severe anemia, regimen 2 subgroups) were also excluded from analysis. First we studied the difference in hs-CRP values in different subgroups formed based on certain characteristics of patient. This was done using independent sample *t*-test (for parameters with ≤2 patient subgroups) and ANOVA test (for parameters with >2 patient subgroups like BMI, duration of illness and stage of disease). Post-hoc analysis was done using Tukey's HSD method, wherever needed.

Results of independent sample *t*-test and ANOVA were as shown in Tables 2 and 3. Apart from CD4 and hemoglobin subgroups, there was no statistically significant ($p > 0.05$) difference in hs-CRP values among the other subgroups formed based on different parameters. Post-hoc analysis revealed that statistically significant ($p < 0.05$) difference in hs-CRP values exists between all the three CD4 subgroups.

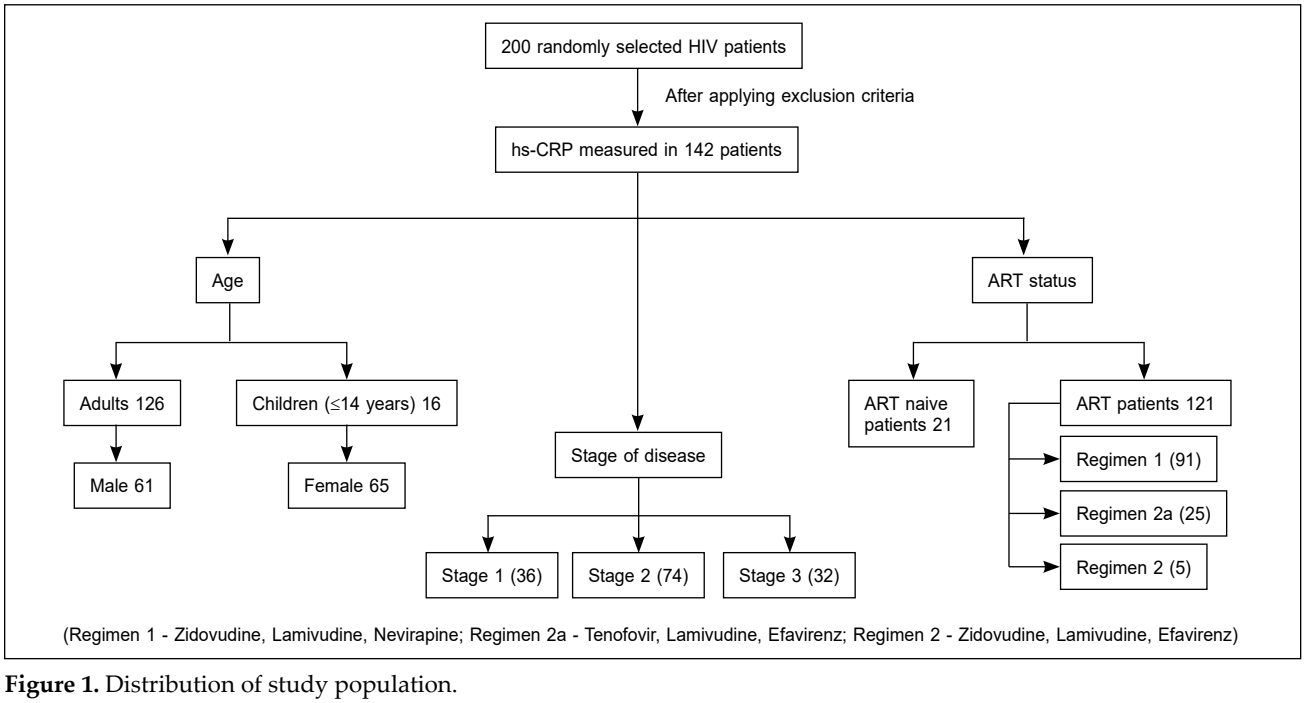

Figure 1. Distribution of study population.

Table 1. Distribution of Study Population-based on hs-CRP Measurements and Baseline Characteristics

Parameter	Subgroups	Low	Average	High	Outliers	Total
Age	Adults	48	41	21	16	126
	Children	41	8	4	1	16
Sex	Male	18	33	8	13	72
	Female	33	16	17	4	70
ART status	Pre-ART	7	2	7	5	21
	On-ART	44	47	18	12	121
Hb level	Normal	42	31	13	5	91
	Mild	5	13	10	12	40
	Moderate	3	4	2	-	9
	Severe	1	1	-	-	2
BMI status	Underweight	1	8	2	5	16
	Normal	39	25	9	11	84
	Overweight	11	16	14	1	42
Duration of illness	<3 years	26	15	13	13	67
	3-5 years	25	23	6	3	48
	≥5 years	6	11	6	1	27
Stages of disease	1	33	11	5	-	36
	2	9	32	11	6	74
	3	2	6	9	11	32
ART regimen	Regimen 1	33	36	14	8	91
	Regimen 2a	9	9	4	3	25
	Regimen 2	2	2	1	-	5
CD4 count	>500	21	10	-	-	31
	200-500	29	31	17	4	81
	≤200	1	8	8	13	30

Table 2. Results of Independent Sample *t*-test

Parameter	Subgroups	hs-CRP				
		N	Mean	*t*	df	P
Age	Adults	110	1.96 (1.63)	0.17	123	0.87
	Children	15	2.80 (2.64)			
Sex	Male	59	2.10 (1.70)	0.201	123	0.841
	Female	66	2.03 (1.88)			
ART status	ART	109	1.98 (1.63)	1.394	123	0.166
	Pre-ART	16	2.64 (2.66)			
Hb	Normal	86	1.78 (1.47)	-3.226	112	0.002
	Mild anemia	28	3.02 (2.47)			
ART regimen	Regimen 1	83	1.93 (1.50)	-0.131	104	0.896
	Regimen 2a	23	1.98 (1.41)			

Table 3. Results of ANOVA

Parameter	Subgroups	hs-CRP				
		N	Mean (SD)	F	df	P
BMI	Underweight	11	2.02 (0.92)	2.60	2	0.78
	Normal	73	1.78 (1.87)			
	Overweight	41	2.57 (1.75)			
DOI	<3 years	54	1.96 (1.74)	1.61	2	0.852
	3-5 years	45	2.14 (1.96)			
	>5 years	26	2.15 (1.65)			
Stages	1	36	1.88 (1.94)	1.328	2	0.269
	2	68	1.98 (1.71)			
	3	21	2.63 (1.77)			
CD4 count	<200	17	3.69 (2.65)	14.14	2	<0.001
	200-500	77	2.10 (1.61)			
	>500	31	1.08 (0.71)			

Correlation of hs-CRP with CD4 Count

The main objective of our study was to find whether there is any correlation of hs-CRP with CD4 levels. This was done using nonparametric Spearman's correlation coefficient test. The correlation between hs-CRP and CD4 was also tested in different subgroups.

Using Spearman's correlation coefficient test, the correlation coefficient between hs-CRP and CD4 count was found to be -0.555 with a statistically significant p value <0.001. This reflects the presence of statistically significant strong negative correlation between hs-CRP and CD4 count. Figure 2 shows the scatter plot showing the correlation between hs-CRP and CD4 count.

The correlation between hs-CRP and CD4 count was tested separately with respect to different parameters. The statistically significant ($p < 0.05$) negative correlation between hs-CRP and CD4 count persisted with respect to different parameters as shown in the Table 4 except in underweight patients. The negative correlation in underweight patients did not reach statistical significance ($p > 0.05$). However, there were only 11 patients in this category.

The negative correlation was stronger

- In adults ($p < 0.001$ and cc = -0.570) than in children ($p = 0.018$, cc = - 0.602)
- In female ($p < 0.001$ and cc = -0.707) than in male ($p = 0.004$, cc = -0.371).
- In normal BMI subgroup ($p < 0.001$, cc = -0.640) than in overweight subgroup ($p = 0.017$, cc = -0.424).

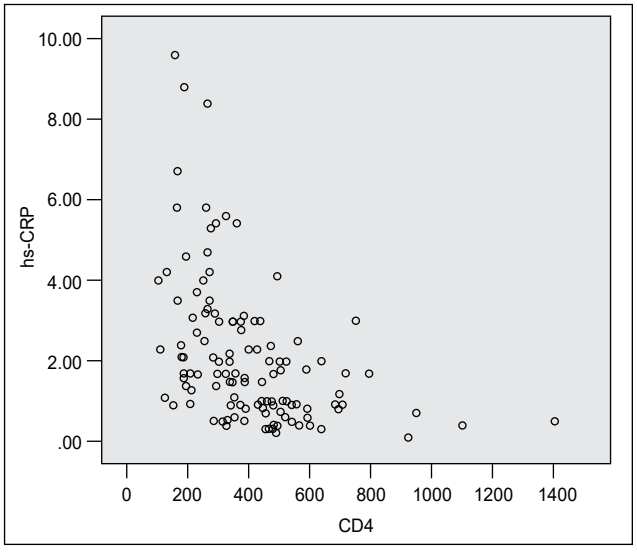

Figure 2. Scatter plot showing correlation of hs-CRP with CD4 count.

Here the dependent variable (Y axis) is hs-CRP and the independent variable (X axis) is CD4 count. Note the peaking of the plot towards the left side indicating the raising hs-CRP with lower CD4 count.

- In ART patients ($p < 0.001$, cc = -0.557) than in pre-ART patients (p value = 0.025, cc = -0.556).
- In patients with duration of illness <3 years ($p < 0.001$, cc = -0.622) and 3-5 years ($p < 0.001$, cc = -0.541) than in patients with duration of illness >5 years ($p = 0.012$, cc = -0.483).
- In patients with Stage 1 ($p = 0.001$, cc = -0.548) and Stage 2 disease ($p < 0.001$, cc = -0.481) than in patients with Stage 3 disease ($p = 0.010$, cc = -0.547).

Table 4. Correlation of hs-CRP with CD4 with Respect to Different Parameters

Parameters	Subgroup	P value	Spearman's coefficient
Age	Children	0.018	-0.602
	Adults	<0.001	-0.570
Sex	Male	0.004	-0.371
	Female	<0.001	-0.707
ART status	Pre-ART	0.025	-0.556
	ART	<0.001	-0.557
Duration of illness	<3 years	<0.001	-0.622
	3-5 years	<0.001	-0.541
	>5 years	0.012	-0.483
BMI	Underweight	0.155	-0.460
	Normal	<0.001	-0.640
	Overweight	0.017	-0.424
Stages of disease	1	0.001	-0.548
	2	<0.001	-0.649
	3	0.010	-0.500
ART regimen	Regimen 1	<0.001	-0.542
	Regimen 2a	0.001	-0.649
Hb levels	Normal	<0.001	-0.481
	Mild	<0.001	-0.674

- In patients on Regimen 1 ($p < 0.001$, cc = -0.542) than in patients on Regimen 2a ($p = 0.001$, cc = -0.649).
- The correlation between hs-CRP and CD4 count was equally stronger in patients with normal hemoglobin ($p < 0.001$, cc = -0.481) and mildly anemic patients ($p < 0.001$, cc = -0.674).

DISCUSSION

The AHA defines risk grade in hs-CRP as <1 mg/L (low risk), 1-3 mg/L (average risk), >3-10 mg/L (high risk) and >10 mg/L (Outlier; suggestive of other inflammatory processes). In assessing cardiovascular disease risk, the AHA recommends that hs-CRP >10 mg/L be discarded and repeated because extremely high hs-CRP values may reflect other processes such as acute infection or other inflammatory processes.[8] In our study, we followed the same protocol for grouping patients based on hs-CRP. Our study had 17 outliers out of the 142 patients. The outliers were excluded from all statistical analysis done in this study.

In our study, there was no statistically significant ($p > 0.05$) difference in hs-CRP values between the <15 years and >15 years age group. This finding was also observed in a study of 97 HIV patients by Zhou et al published in 2015.[9] But, a study from Sao Paulo in Brazil by Riberio (1997) with a sample size of 165 adults and 125 children showed a significant difference in CRP levels measured by enzyme-linked immunosorbent assay (ELISA) between healthy children and adults.[10] It should be noted that the sample size of <15 years patients in our study was very small. Further we measured hs-CRP and not just CRP.

There was no significant ($p > 0.05$) difference between hs-CRP levels in both sexes in our study. Similar findings were noted in the study by Zhou et al in 2015.[9] However, in a study by Shikuma et al in 2011,[7] there was significant difference in hs-CRP levels between male and female patients following initiation of efavirenz-based ART. Gender differences in hs-CRP have been reported in the general population. Women with National Cholesterol Education Program (NCEP)-defined metabolic syndrome have higher hs-CRP levels compared to men with the metabolic syndrome.[11] One of the important finding in our study was that there was no significant difference ($p > 0.05$) in hs-CRP levels between patients on ART and ART-naïve patients. This is in contradiction to findings from earlier studies probably because of small sample size (15%) of pre-ART patients in our study. In a study by Noursadeghi

et al published in 2005 approximately 30% of patients with HIV receiving long-term ART were shown to have CRP levels >3.0 mg/L,[12] the highest CRP levels being observed in those who were currently treated with ART.[13] Furthermore, elevated hs-CRP levels have been observed in ART-treated compared with ART-naïve HIV-positive patients in another study by Guimarães et al published in 2008.[14] Changes in CRP levels following protease inhibitor (PI) therapy were studied in the AIDS Clinical Trials Group (ACTG) 5056s. This study assessed changes in CRP levels following indinavir-based highly active antiretroviral therapy (HAART) and noted that CRP levels remained stable or decreased slightly over an average of 42 months.[15] A similar slight decline overall was seen in the HIV Study with Epzicom And Truvada (HEAT) study over 96 weeks following initiation of lopinavir and ritonavir given with either ABC/3TC or tenofovir/emtricitabine.[16] The overall trend of decreasing CRP levels over time in both studies was observed only in men. On the contrary to both these studies, continuation of ACTG 5056 by Shikuma et al in 2011 utilizing NNRTI-based HAART over 96 weeks found a slight statistically insignificant increase in hs-CRP in men but a significant increase in hs-CRP in women.[7]

Another interesting finding from our study was that there was no statistically significant ($p > 0.05$) difference in hs-CRP levels between patients on different ART regimen. Majority of our patients were taking NACO Regimen 1 consisting of zidovudine, lamivudine and nevirapine. Nine patients were taking Regimen 2a consisting of tenofovir, lamivudine and efavirenz. Only 2 patients were taking Regimen 2 consisting of zidovudine, lamivudine and efavirenz. Most of the studies have studied the change in hs-CRP levels with the introduction of different ART regimen like the ACTG 5059 or HEAT study. But these studies did not directly compare the hs-CRP levels in patients on different ART regimen. In 2014, Hattab et al published their study that compared the change in inflammatory markers including hs-CRP from the baseline 2 years following the start of two different ART regimens. In this study, they found that hs-CRP levels fell slightly although not significantly from the pre-ART period, but there was no differential effect of the studied antiretroviral drugs regimen on hs-CRP levels.[17] Further Boger et al in 2009 did not find a difference in hs-CRP in subjects on PI versus non-PI-based ART.[18] These were in accordance with our study results.

In our study, significant difference in hs-CRP levels in different BMI groups was noted even after patients with BMI in the obesity range (>27.5 kg/m^2) were excluded from the study. Post-hoc analysis of ANOVA results by Tukey's HSD test found out that there was significant ($p = 0.031$) difference in hs-CRP levels between the normal (BMI - 18.5 to 23 kg/m^2) and overweight (BMI - 23 to 27.5 kg/m^2) group. High BMI is a known risk factor for increased hs-CRP in general population. This was also confirmed in HIV patients by Boger et al in 2009.[18]

There was significant difference ($p = 0.012$) in hs-CRP levels between patients with normal hemoglobin and mild anemia in our study. This is in stark contrast to the findings in a study by Wisaksana et al in 2011 in HIV patients from Indonesia, which showed no correlation of hs-CRP with serum ferritin levels or degree of anemia.[19] We found that there was no statistically significant difference ($p > 0.05$) in hs-CRP levels in patients with varying duration of illness with or without ART. For our analysis, we divided our study population into three groups based on the duration of illness from the time of initial diagnosis: <3 years, 3-5 years and >5 years. We found no difference in hs-CRP levels between these three groups with no regards to whether or not they were on any ART regimen. Also, we found that there was no significant ($p > 0.05$) difference in hs-CRP levels with respect to WHO stages of HIV infection. It is to be noted that we had not included patients with Stage 4 HIV in our study. Only patients in Stage 1, 2 or 3 were included. We could not find any study done earlier that could support or refute these two findings.

Using Spearman's correlation test, we found a statistically significant negative correlation between hs-CRP and CD4 counts of our study population with both parameters taken as continuous variable. The correlation coefficient was -0.555 with p value <0.001. This correlation was also tested in different subpopulation within our study divided based on the parameters as mentioned earlier. The negative correlation between hs-CRP and CD4 count was noted in all of the above mentioned subpopulation and it was statistically significant ($p < 0.05$) in all except in subgroup with underweight ($p = 0.155$, cc = -0.460) patients.

In an article published by Guimarães et al in 2008 assessing the hs-CRP levels in 171 HIV-infected patients treated (n = 129) or not with antiretroviral drugs (n = 42) and their correlation with factors related to cardiovascular risk and HIV infection, no correlation was found between hs-CRP levels and CD4 cell counts and HIV-viral load.[14]

Despite extensive research we could not find a similar study with similar objectives, probably because we already have a reliable marker for disease monitoring in HIV patients in the form of CD4 count estimation. Studies are usually done to find out other effective markers that can supersede already existing one and are not done to test the efficacy of a less reliable marker such as hs-CRP, which probably could never be more reliable than a disease-specific marker such as CD4 count. Efforts are already on to phase in HIV RNA levels in place CD4 count estimation as HIV RNA assays are more efficacious than CD4 count for disease monitoring.

However, developing nations of South-East Asia and Africa are still struggling to economically account for growing demands of HIV care including routine 6-monthly CD4 estimation for disease monitoring. In such resource, poor setting hs-CRP measurements could come in handy as a cheaper relatively reliable marker for monitoring disease activity. Hence, our study could be regarded as a pioneer study in this regard. Until now, majority of studies concerned with measuring hs-CRP in HIV patients have studied only its potential role as an independent risk factor for cardiovascular disease in HIV patients. Few studies done in Africa have studied hs-CRP as a marker of disease progression in HIV patients[20] and for predicting HIV-related outcomes.[21]

CONCLUSION AND DRAWBACKS

To conclude, with this study we set out to explore the possibility of serum hs-CRP levels as a tool for monitoring of disease activity in HIV-infected patients. We decided to correlate hs-CRP levels with an already existing reliable marker of HIV disease progression i.e., CD4 count, to look for any linear relationship between the two markers. The major inspiration for this study was two studies from Africa. One by Drain et al, 2007[21] who found CRP to be a cheaper tool that could predict HIV-related outcomes among women and children in a resource poor setting of Tanzania. The other study was published in 2010 by Redd et al[20] who found the rise in CRP levels during HIV-1 disease progression despite the absence of microbial translocation in Rakai, Uganda.

The popular perception that CRP levels will be increased invariably in HIV patients irrespective of disease activity due to presence of other opportunistic infection cannot be entirely true. Not all HIV patients will harbor opportunistic infection at all times in their disease course. With advanced HAART, now more and more patients are going in for long-term remission. We believe that hs-CRP has the potential to be a cheaper alternate disease activity marker in place of CD4 count in this population of patients with long-term remission.

We found a significant negative correlation between the hs-CRP levels and CD4 count i.e., with decreasing CD4 count, hs-CRP showed increasing trend. This is in contrast to previous studies that showed no correlation between the two. This result could be regarded as a small stepping stone towards our study goal. However, our study was done in a single center and it was a cross-sectional study. Multicenter, follow-up studies are required in future to fully explore the possibility of hs-CRP as a replacement marker in place of CD4 count for monitoring of HIV patients.

Our study was a cross-sectional study, and the study design was appropriate for the study's objective which was determining hs-CRP levels in HIV-infected patients and assessing correlation if any that exists between measured hs-CRP levels and CD4 count of the patient. But our design may not be ideal for our study goal which is to assess the potential of hs-CRP levels as a replacement marker in place of CD4 count for monitoring disease progression in HIV patients, which requires long-term follow-up and serial simultaneous measurement of both hs-CRP and CD4 count to determine whether the observed correlation between the two is repeatable and reproducible. This was not done in our study due to economic and time restraints.

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"No one should die of heart disease just because he/she cannot afford it"

About Sameer Malik Heart Care Foundation Fund

"Sameer Malik Heart Care Foundation Fund" it is an initiative of the Heart Care Foundation of India created with an objective to cater to the heart care needs of people.

Objectives

- Assist heart patients belonging to economically weaker sections of the society in getting affordable and quality treatment.
- Raise awareness about the fundamental right of individuals to medical treatment irrespective of their religion or economical background.
- Sensitize the central and state government about the need for a National Cardiovascular Disease Control Program.
- Encourage and involve key stakeholders such as other NGOs, private institutions and individual to help reduce the number of deaths due to heart disease in the country.
- To promote heart care research in India.
- To promote and train hands-only CPR.

Activities of the Fund

Financial Assistance

Financial assistance is given to eligible non emergent heart patients. Apart from its own resources, the fund raises money through donations, aid from individuals, organizations, professional bodies, associations and other philanthropic organizations, etc.

After the sanction of grant, the fund members facilitate the patient in getting his/her heart intervention done at state of art heart hospitals in Delhi NCR like Medanta – The Medicity, National Heart Institute, All India Institute of Medical Sciences (AIIMS), RML Hospital, GB Pant Hospital, Jaipur Golden Hospital, etc. The money is transferred directly to the concerned hospital where surgery is to be done.

Drug Subsidy

The HCFI Fund has tied up with Helpline Pharmacy in Delhi to facilitate patients with medicines at highly discounted rates (up to 50%) post surgery.

The HCFI Fund has also tied up for providing up to 50% discount on imaging (CT, MR, CT angiography, etc.)

Who is Eligible?

All heart patients who need pacemakers, valve replacement, bypass surgery, surgery for congenital heart diseases, etc. are eligible to apply for assistance from the Fund. The Application form can be downloaded from the website of the Fund. http://heartcarefoundationfund.heartcarefoundation.org and submitted in the HCFI Fund office.

Important Notes

- The patient must be a citizen of India with valid Voter ID Card/ Aadhaar Card/Driving License.
- The patient must be needy and underprivileged, to be assessed by Fund Committee.
- The HCFI Fund reserves the right to accept/reject any application for financial assistance without assigning any reasons thereof.
- The review of applications may take 4-6 weeks.
- All applications are judged on merit by a Medical Advisory Board who meet every Tuesday and decide on the acceptance/rejection of applications.
- The HCFI Fund is not responsible for failure of treatment/death of patient during or after the treatment has been rendered to the patient at designated hospitals.
- The HCFI Fund reserves the right to advise/direct the beneficiary to the designated hospital for the treatment.
- The financial assistance granted will be given directly to the treating hospital/medical center.
- The HCFI Fund has the right to print/publish/webcast/web post details of the patient including photos, and other details. (Under taking needs to be given to the HCFI Fund to publish the medical details so that more people can be benefitted).
- The HCFI Fund does not provide assistance for any emergent heart interventions.

Check List of Documents to be Submitted with Application Form

- Passport size photo of the patient and the family
- A copy of medical records
- Identity proof with proof of residence
- Income proof (preferably given by SDM)
- BPL Card (If Card holder)
- Details of financial assistance taken/applied from other sources (Prime Minister's Relief Fund, National Illness Assistance Fund Ministry of Health Govt of India, Rotary Relief Fund, Delhi Arogya Kosh, Delhi Arogya Nidhi), etc., if anyone.

Free Diagnostic Facility

The Fund has installed the latest State-of-the-Art 3 D Color Doppler EPIQ 7C Philips at E – 219, Greater Kailash, Part 1, New Delhi.
This machine is used to screen children and adult patients for any heart disease.

Free Education and Employment Facility

HCFI has tied up with a leading educational institution and an export house in Delhi NCR to adopt and to provide free education and employment opportunities to needy heart patients post surgery. Girls and women will be preferred.

Laboratory Subsidy

HCFI has also tied up with leading laboratories in Delhi to give up to 50% discounts on all pathological lab tests.

Help Us to Save Lives

The Foundation seeks support, donations and contributions from individuals, organizations and establishments both private and governmental in its endeavor to reduce the number of deaths due to heart disease in the country. All donations made towards the Heart Care Foundation Fund are exempted from tax under Section 80 G of the IT Act (1961) within India. The Fund is also eligible for overseas donations under FCRA Registration (Reg. No 231650979). The objectives and activities of the trust are charitable within the meaning of 2 (15) of the IT Act 1961.

Donate Now...

About Heart Care Foundation of India

Heart Care Foundation of India was founded in 1986 as a National Charitable Trust with the basic objective of creating awareness about all aspects of health for people from all walks of life incorporating all pathies using low-cost infotainment modules under one roof.

HCFI is the only NGO in the country on whose community-based health awareness events, the Government of India has released two commemorative national stamps (Rs 1 in 1991 on Run For The Heart and Rs 6.50 in 1993 on Heart Care Festival- First Perfect Health Mela). In February 2012, Government of Rajasthan also released one Cancellation stamp for organizing the first mega health camp at Ajmer.

Objectives

- Preventive Health Care Education
- Perfect Health Mela
- Providing Financial Support for Heart Care Interventions
- Reversal of Sudden Cardiac Death Through CPR-10 Training Workshops
- Research in Heart Care

Heart Care Foundation Blood Donation Camps

The Heart Care Foundation organizes regular blood donation camps. The blood collected is used for patients undergoing heart surgeries in various institutions across Delhi.

Committee Members

Chief Patron

Raghu Kataria

Entrepreneur

President

Dr KK Aggarwal

Padma Shri, Dr BC Roy National & DST National Science Communication Awardee

Governing Council Members

Sumi Malik
Vivek Kumar
Karna Chopra
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Nilesh Aggarwal
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Advisors

Mukul Rohtagi
Ashok Chakradhar

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Deep Malik
Geeta Anand
Dr Uday Kakroo
Harish Malik
Aarti Upadhyay
Raj Kumar Daga
Shalin Kataria
Anisha Kataria
Vishnu Sureka
Rishab Soni

This Fund is dedicated to the memory of **Sameer Malik** who was an unfortunate victim of sudden cardiac death at a young age.

- HCFI has associated with Shree Cement Ltd. for newspaper and outdoor publicity campaign
- HCFI also provides Free ambulance services for adopted heart patients
- HCFI has also tied up with Manav Ashray to provide free/highly subsidized accommodation to heart patients & their families visiting Delhi for treatment.

Indian Journal of Clinical Practice, Vol. 31, No. 4, September 2020

Effect of Protein and Energy Supplementation on Growth of Infants ≤1,500 g at Birth: A Randomized Trial

JANARDHAN SHENOY*, NIVETHITHA†, SUCHETHA RAO*

ABSTRACT

Objective: To study the effect of energy supplements with protein-energy supplementations on the growth patterns of low birth weight (LBW) infants weighing ≤1,500 g. **Material and methods:** Babies with birth weight of ≤1,500 g and on full enteral feeds on Day 14 of life with expressed breast milk (n = 60) were randomly allocated to energy alone group (n = 30) and protein-energy group (n = 30). Babies in energy intervention received medium-chain triglyceride and protein-energy intervention received human milk fortifier supplement added to expressed breast milk. Daily weight, weekly length and head circumference were checked to monitor the growth. Study was continued till the infants reached a weight of 1,600 g or 4 weeks from the start of the study, whichever was earlier. **Results:** In the energy group, mean weight gain was 14.98 ± 0.09968 g/kg/day, whereas in the protein-energy group weight gain was 19.79 ± 0.08745 g/kg/day ($p < 0.001$). Increase in length or head circumference did not show any statistical significance. **Conclusion:** This study was consistent with the importance of providing additional protein intake to achieve increased postnatal growth in LBW babies.

Keywords: Low birth weight, feeding, protein-energy supplements

Nutritional management of the very low birth weight (VLBW) infants is quite a challenge for present neonatal intensive care unit (NICU) teams.[1] Most VLBW infants have discharge weight below the 10th percentile of reference intrauterine weights leading to postnatal growth restriction.[2,3] Poor neonatal weight gain and head growth have been linked to significant neurodevelopmental outcomes. Interventions to improve antenatal and postnatal growth may contribute to better school-age outcomes.[4] To achieve the necessary catch-up growth, nutritional supplements have been added to standard preterm formula or fortified human milk.[1] Preterm infants inevitably accumulate a significant nutrient deficit in the first few weeks of life, if fed only with recommended daily allowance of nutrients. This deficit can be directly related to subsequent postnatal growth retardation.[3] We conducted a randomized controlled trial to study the effect of energy supplements with protein-energy supplementations on the growth patterns of low birth weight (LBW) infants weighing ≤1,500 g.

MATERIAL AND METHODS

It was a prospective, randomized controlled trial done in a tertiary care hospital in Dakshina Kannada district of Karnataka. The study was conducted from March 2011 to July 2012. After getting parental consent, babies with birth weight of ≤1,500 g and on full enteral feeds on Day 14 of life were included in the study. Babies with major congenital malformation, suspected or confirmed necrotizing enterocolitis, requiring major surgery, genetic defects, congenital infection, suspected inborn errors of metabolism and on formula feeding were excluded from the study. Study was conducted after Institutional Ethical Committee clearance. A total of 70 infants were included in the study. Infants were randomly assigned into two groups using randomization table, either protein and energy group or energy alone group. Each group comprised of 35 infants. They were

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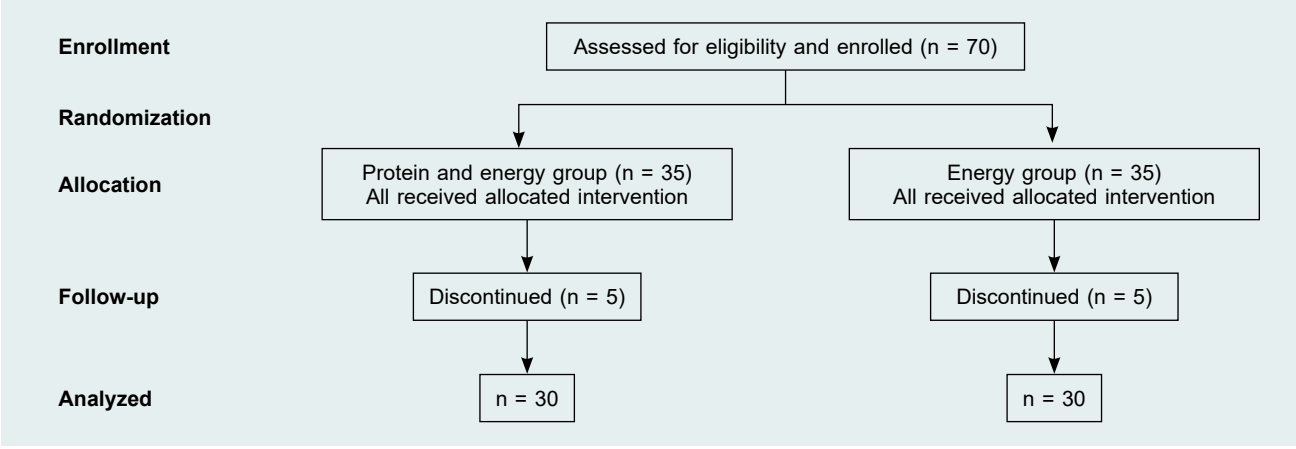

categorized into appropriate-for-gestational age (AGA) or small-for-gestational age (SGA) in each group. Study was continued till the infants reached a weight of 1,600 g or 4 weeks from the start of the study, whichever was earlier. Babies developing any feed intolerance or any other complications were excluded from the study. Five babies from each group were excluded during the course of the study due to feed intolerance and insufficient lactation in the mother. Thirty babies in each group were finally analyzed. Babies were feed through nasogastric tube every 2 hours. Trained nurse fed the babies.

Those babies randomized to the energy-alone intervention received medium-chain triglyceride (MCT). Each milliliter of MCT oil was added to 50 mL of expressed breast milk (EBM). Those babies randomized to protein-energy intervention received human milk fortifier (HMF). One sachet of 2 g of HMF was added to 50 mL of expressed milk. All babies receiving protein-energy and energy alone supplement had received only mother's milk. Protein and calorie content per 100 mL of breast milk given to each group is shown in Table 1.

Babies were managed in the same postnatal ward with same ambient temperature. Babies of both groups were provided with cap, gloves, socks and they were rapped with cotton sheet and covered with blankets to prevent the heat loss.

Growth rate was measured during the study period by:

- Daily weights by electronic weighing machine (Jee-lit with an error of 10 g). The weight was recorded at the same time of the day in all babies.
- Weekly length by infantometer
- Weekly head circumference by nonstretchable inch/centimeter tape.

Table 1. Comparison of Caloric and Protein Content of Breast Milk With and Without Nutritional Supplements

	Calories (kcal) per 100 mL	Protein (g) per 100 mL
Human milk	68	1.1
Human milk + MCT	83.4	1.1
Human milk + HMF	82.94	1.5

Mean weight gain in grams per kg per day was calculated by subtracting first day weight from last day weight and dividing it by total number of days and birth weight.

RESULTS

Thirty-five babies were included to energy alone group and 35 babies to energy and protein group in the beginning of the study. Five babies from each group were excluded during the course of the study due to feed intolerance and insufficient lactation in the mother. Thirty babies in each group were finally analyzed. Birth weight, gestational age, gender and other baseline characteristics did not differ significantly between two groups (Table 2).

There was no significant difference in weight gain between male and female babies in this study. The weight gain in the infants receiving protein-energy supplementation was significantly better than those receiving energy alone group (Table 3). In the energy group, mean weight gain was 14.98 ± 0.09968 g/kg/day, whereas in the protein-energy group weight gain was 19.79 ± 0.08745 g/kg/day ($p < 0.001$). The infants randomized to protein-energy group regained the birth weight and target weight faster than energy alone group but this was not statistically significant. Energy

Table 2. Baseline Characteristics of Each Group

Variables	Energy alone group (MCT) (n = 30)	Protein and energy group (HMF) (n = 30)	P value
Mean birth weight (grams)	1.26	1.19	0.678
Mean gestational age (weeks)	32.94	32.5	0.996
SGA	18 (60%)	17 (57%)	0.943
Gender (males)	16 (53%)	18 (60%)	0.865

Table 3. Outcome of Nutritional Intervention

Parameters	Energy alone group (MCT) (n = 30) mean ± SD	Protein and energy group (HMF) (n = 30) mean ± SD	P value
Weight gain (g/kg/day)	14.98 ± 0.09968	19.79 ± 0.08745	< 0.001
Length gain (cm/week)	0.375 ± 0.09167	0.402 ± 0.08461	0.632
Head circumference (cm/week)	0.395 ± 0.09534	0.414 ± 0.08567	0.783
Number of days to regain birth weight	8 ± 2.598	4.2 ± 2.856	0.15
Duration of study	25.6 ± 3.67157	21 ± 2.74159	0.19

alone group attained birth weight and target weight in 8 ± 2.598 days and in 25.6 ± 3.6715 days, respectively. Protein-energy group attained birth weight and target weight in 4.4 ± 2.856 days and 21 ± 2.74159 days, respectively. SGA babies gained target weight faster than AGA but without statistical significance. There is no significant difference in weight loss in two groups before including into the study.

Head circumference increased by 0.395 cm/week in energy alone group and 0.414 cm/week in protein-energy alone group. Length increased by 0.375 cm/week in energy alone group and 0.402 cm in protein-energy alone group. Increase in length or head circumference did not show any statistical significance.

DISCUSSION

LBW infant's adaptation to extrauterine life is an energy consumptive process.[5] Postnatal growth retardation is a major issue in preterm infants.[6] Optimizing growth in the preterm infant continues to be a difficult task and is complicated by a lack of knowledge of the optimal growth pattern. Adequate postnatal growth is necessary for optimal neurological outcome. Prevention of postnatal growth failure requires a comprehensive nutritional regimen that provides adequate nutritional support as soon after birth as possible and is maintained throughout an infant's hospital course.[7] The general trend in many of the NICU in the developing countries to increase the postnatal growth of LBW babies is by addition of MCT oil. HMF is not widely used. Addition of HMF will provide energy as well as protein to the growing babies, but MCTs will provide energy alone. Hence, this study was done to compare the effectiveness of protein-energy supplement over energy supplement.

Brumberg et al[1] compared the growth in the babies, those received energy alone with those who received protein and energy supplements. The babies in the energy alone gained 11.5 ± 4.8 g/kg/day and protein-energy group babies gained 17 ± 2.4 g/kg/day.[1] In the present study, babies in the energy alone group gained 14.98 ± 0.09968 g/kg/day and those in protein-energy group gained 19.79 ± 0.08745 g/kg/day.

Gathwala et al[8] studied the effect of HMF supplements in SGA babies. The babies who received fortified milk gained a mean weight of 38.77 ± 7.43 g/day, which was significantly better than expressed milk alone group babies who gained 28.71 ± 3.18 g/day. The present study included both SGA and AGA babies. Mukhopadhyay et al[9] showed that when preterm babies were fed fortified human milk they had better growth and they compared them with mineral supplements. They followed the babies till they reached 2 kg, whereas in our study we followed them till 1.6 kg. On subgroup analysis, they found that SGA preterm babies fed with fortified milk had significantly better growth than those fed unfortified milk as compared to AGA babies. Our study also shows that SGA babies gained faster than the AGA babies but statistically it was not significant. The mean birth weight of the LBW babies in their study was 1.2 kg, which was similar to our study.

Study by Miller et al[10] showed that increasing the protein content of HMF improved the growth of LBW babies of <31 weeks gestation.

Lucas et al[11] showed that developmental scores at 18 months were slightly but not significantly better in the preterm who received protein supplements. Present study has limitation that follow-up was not done.

CONCLUSION

Present study highlights the continued need of enteral protein in growth of VLBW infants. To improve growth in these infants, supplementation of EBM with protein must be considered. This study has shown the growth benefits of increasing caloric intake with a multinutrient supplement that provides both protein and energy compared with a supplement that provides only energy.

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Moderna COVID-19 Vaccine Appears to Work Well in Older Adults

As per Moderna Inc, its experimental COVID-19 vaccine induced immune responses in older adults similar to those observed in younger participants.

The findings raise hope that the vaccine will be effective in people considered to be at high risk for severe complications from COVID-19. Moderna vaccine candidate - mRNA-1273 - is in late-stage human trials. The latest data from an early Phase I study reports on an analysis of 20 additional people describing the vaccine performance in older adults. The analysis evaluated individuals who received the 100-µg dose being tested in the much larger Phase III trial. The immune responses seen in those aged 56-70, above age 70 and those aged 18-55 were found to be similar… (*Reuters*)

CDC Changes COVID-19 Testing Guidance

The US Centers for Disease Control and Prevention (CDC) has changed the COVID-19 recommendations stating that testing for SARS-CoV-2 infection is now optional for asymptomatic individuals, irrespective of potential personal exposure.

The updated guidance states that an individual does not necessarily need a test unless he/she is a vulnerable person or his/her healthcare provider or state or local public health official recommends that they undergo a test. According to the updated CDC guidance, if a person has been in close contact (within 6 feet) of a person infected with COVID-19 for at least 15 minutes but does not have symptoms, then the person does not necessarily require a test… (*Medscape*)

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Harboring a Neglected Metallic Foreign Body in Maxillofacial Region for 12 Years

JEEWAN BANIYA*, NARMAYA THAPA†, URMILA GURUNG‡

ABSTRACT

Penetrating injuries to the maxillofacial region are common. These injuries always create a challenge to ear, nose and throat surgeons or maxillofacial surgeons to remove, especially when the foreign body lies deep in the maxillofacial region. These foreign bodies result in pain, bleeding and infection and are removed immediately. Occasionally, the foreign body, without serious symptoms, can remain for several years without treatment. We present a case of a 59-year-old man with a metallic foreign body in the right maxillofacial region who had a history of trauma on right cheek by an unknown object during insurgency 12 years back and successful removal was done via an external approach.

Keywords: Foreign body, maxillofacial, removal

Foreign bodies are often encountered by ear, nose and throat surgeons and oral and maxillofacial surgeons and can present as a diagnostic and therapeutic challenge to the surgeon due to factors like the size of the object, difficulty in access and a close anatomic proximity of the foreign body to vital structures. Any penetrating injury in the head and neck region should prompt evaluation for the presence of a foreign body. About a third of all foreign bodies are often missed at the time of initial examination. These foreign bodies may remain dormant in the soft tissue for years altogether without causing any significant damage to the adjacent structures. However, some of them can cause chronic inflammatory reaction leading to distressing symptoms. Diagnosis of these cases is often based on the presence of associated pain and swelling. Radiologic workup, basically computed tomography (CT), has principal role in the diagnosis of such cases. The foreign body can often modify the regional anatomy, which is mainly seen in high velocity wounds. Similarly, the inflammatory response in the tissues around a foreign body can pose difficulties in its removal.

This case report highlights the successful removal of neglected foreign body in the maxillofacial region impacted for 12 years.

CASE REPORT

A 59-year-old male patient had been having long-standing right cheek swelling of 12 years, which was preceded by an accidental injury with an unknown object during insurgency period. The wound was sutured at a local health post then with no further evaluation as the patient resided in a rural area. The same incident had left him with a decreased vision on the right side. Since the past 2 months, he started having pain and non-foul smelling discharge from the right cheek, which made him seek medical attention.

These current symptoms were not associated with fever, difficulty opening mouth, dental pain, loosening of tooth, decreased sensation over right cheek or any nasal symptoms. Chronic illnesses like diabetes mellitus, tuberculosis or any immune compromised status were absent. There was a history of alcohol intake but no history of smoking.

Complete ear, nose and throat examination revealed diffuse, nonfluctuant swelling over right cheek and infratemporal region with tender, erythematous area in anterior part of the cheek along with a curvilinear scar

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measuring around 3 cm involving the entire length of right ala of nose and extending to right cheek blunting the right alar crease. There were two discharging pits close by each other in the right side of the scar (Fig. 1). Movement of right eyeball was restricted in all directions with blunted right infraorbital rim. There was only perception of light on right eye. Nasal endoscopy was normal without any mass or purulent discharge. Other ear, nose and throat examinations were normal. Informed consent for the photography was taken from the patient.

Plain CT of nose and paranasal sinus showed fracture of right zygomatic and maxillary bone including zygomatic arch and floor of orbit with displacement of orbital contents inferiorly. There was cortical irregularity predominantly in maxillary bone with abscess and sinus tract formation suggesting chronic osteomyelitis with abscess formation. The study was limited due to streak artifacts by metallic foreign body (Fig. 2). However, 3-dimensional reconstruction of CT revealed obliquely lying foreign body just above the ramus of mandible on right side with fractured zygomatic bone, zygomatic arch and inferolateral wall of orbit. Anterolateral wall of the right maxillary sinus was fractured and was pushed medially causing narrowing of the maxillary sinus (Fig. 3).

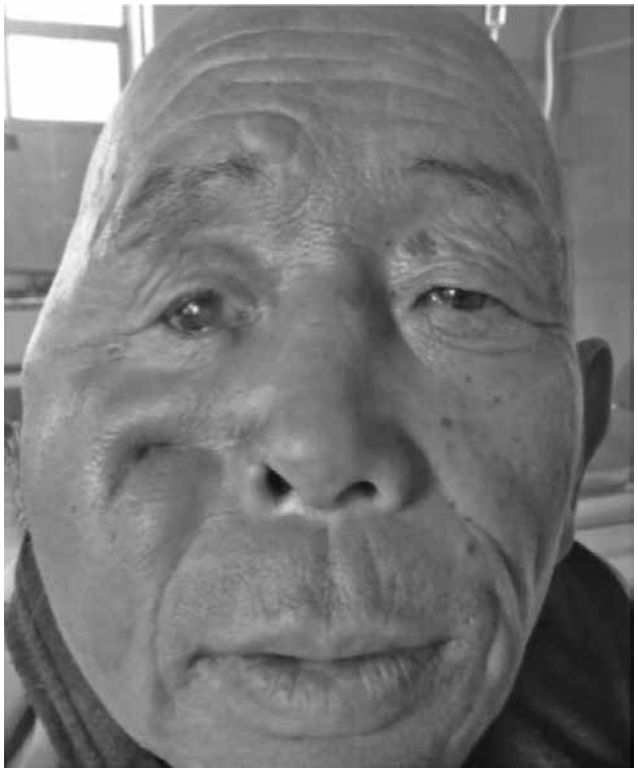

Figure 1. Preoperative photograph of the patient showing swelling of right cheek and scar with discharging pit.

The pus culture sensitivity from the sinus showed no growth. All routine investigations and investigations regarding general anesthesia (GA) fitness were normal.

Exploration and foreign body removal with debridement under GA was then planned.

Peroperatively, Weber Ferguson incision was given with lateral extension 5 cm from the lateral canthus followed by approximately 4 cm inferiorly up to the level of tragus. A separate incision around the site of discharging pit was made and excised. Subcutaneous flap was elevated (Fig. 4 a and b). Intraoperatively, there was a crescent-shaped metallic foreign body impacted in the anterolateral wall of right maxillary sinus just

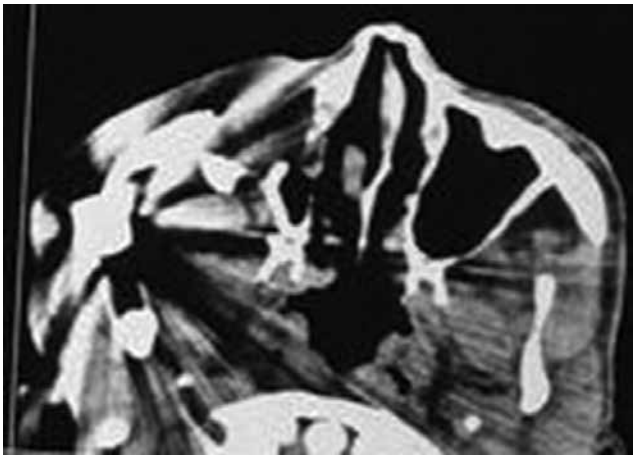

Figure 2. CT of nose and paranasal sinus showing foreign body lateral to the ramus of mandible on right side with streak artifact.

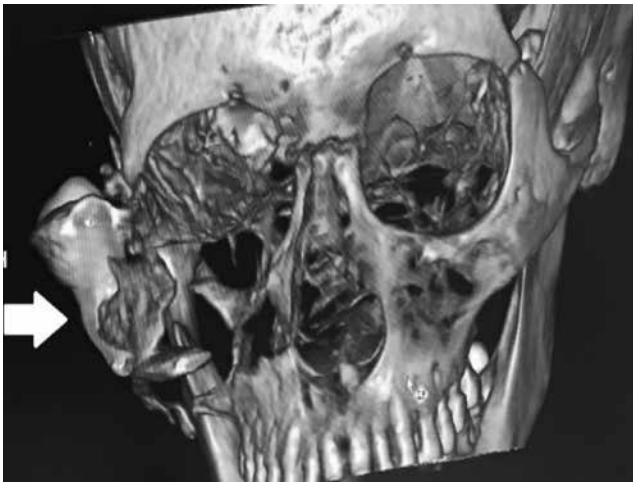

Figure 3. Three-dimensional reconstruction CT scan showing a foreign body (shown by *white arrow*) placed obliquely above the ramus of mandible on right side with fractured zygomatic bone, zygomatic arch and inferolateral wall of orbit along with fracture of anterolateral wall of right maxillary sinus resulting in narrowing of maxillary sinus.

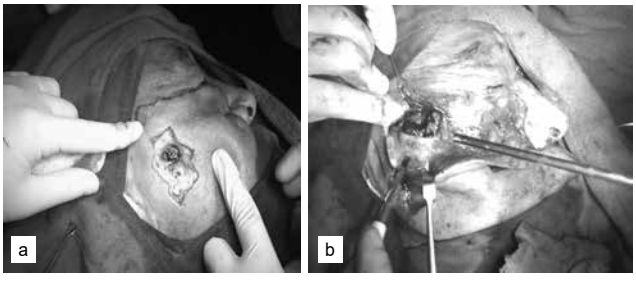

Figure 4. Intraoperative photograph of incision and foreign body **(a)** and metallic irregular foreign body impacted through the right maxillary bone just above the body of mandible with minimal pus **(b)**.

Figure 5. Photograph showing the retrieved foreign body.

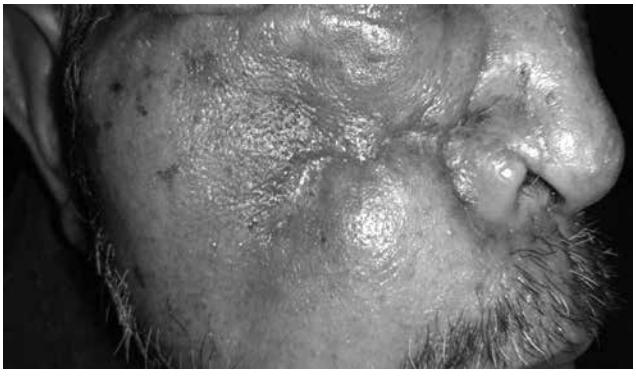

Figure 6. Postoperative photograph showing healed incision site at 18th postoperative day.

superior to the body of the right mandible placed obliquely and extending up to the temporomandibular joint. Foreign body measuring 6.5 × 3 cm was removed followed by debridement of surrounding unhealthy bone (Fig. 5). The maxillary sinus was opened and the tract extending from the lodgment of foreign body to the scar on anterior part of the cheek was removed. Hemostatic agents were used to obliterate the dead space created after removal of foreign body and debridement. The wound was then closed in 3 layers using absorbable suture in inner two layers and nonabsorbable suture in skin, followed by application of compression dressing.

Apart from serosanguineous discharge from the wound on the cheek noted on 3rd postoperative day that settled on 15th postoperative day with daily compression dressing, the postoperative period was uneventful. The patient received postoperative intravenous (IV) antibiotics for 14 days. The patient was discharged following suture removal on 18th postoperative day (Fig. 6).

DISCUSSION

Despite having a complex anatomy, foreign body impaction is not common in the maxillofacial region. The incidence of traumatic penetrating foreign body in maxillofacial region of the body has become common in past few decades owing to road traffic accidents and gunshot wounds. Many important nerves and vessels lie in the maxillofacial region.

Pieces of metallic objects, broken wood, twigs, bamboo splinter, glass particles, tooth brush, fish hook, pen cap with spring and fragments of smoking pipe are some foreign bodies that get impacted commonly in the maxillofacial region. It is possible for foreign objects to penetrate deep into soft and hard tissues through open wounds and lacerations sustained during trauma. If left undiagnosed, these foreign bodies can lead to serious complications within days, months or even years following the initial trauma.

A nonhealing wound that has occurred as a result of penetrating injury and shows continuous purulent discharge, having pain or developing a chronic draining sinus, should be suspected for the presence of a retained foreign body. These foreign bodies and the associated inflammatory reaction have the potential to migrate to infratemporal fossa and through other foramina, and cause life-threatening complications such as hemorrhage, blindness and intracranial complications. Foreign bodies are often antigenic and incite chronic inflammatory responses. The magnitude of an inflammatory reaction is determined by the chemical composition and physical form of the foreign bodies. However, some long-standing foreign bodies may remain clinically silent surprisingly. In a case report by Fernandes and Fernandes, of a 50-year-old male with a history of gunshot, the foreign body was clinically silent without any symptoms or signs for 12 years. Similarly, incidental finding of multiple foreign body pellets following ballistic injury on maxillofacial region 35 years back was published by Rao et al in 2014. Retained

foreign body can undergo two types of foreign body reactions: an aseptic fibrinous response, which gives rise to the formation of a granuloma, which can undergo calcification and decomposition. Such a response is usually clinically silent and incidentally discovered; and an exudative type of inflammatory reaction, resulting in an abscess. In our case, aseptic foreign body reaction with granuloma formation could be the reason for foreign body remaining non-infected for so long.

In our patient, CT images revealed a foreign body in the maxillary region and fracture of zygomaticomaxillary complex. As foreign body was metallic, it was easily detected; however, it is reported that CT cannot detect nonmetallic foreign body like wood, in which only air like radiolucent area is visualized.

In management of impacted foreign bodies, surgical removal is the treatment of choice as they are the potent source of pain and infection. The method of removal is controversial, which depends on size and anatomical location of the foreign body. Various techniques have been described in literature regarding the removal of foreign body. In our case, though the foreign body was easily visualized, it's exact location, size and shape could not be ascertained due to streak artifact. Thus, we followed an external approach for foreign body removal.

Perioperative antibacterial therapy is vital to prevent infections that can occur due to contaminated foreign bodies and should be started early.

In our case also, we kept patient on IV antibiotics before removal of foreign body for 5 days and continued for 2 weeks after removal, followed by daily compression dressing.

CONCLUSION

Neglected foreign body maxilla with fracture of facial bone is rare. We should proceed with radiological workup, preferably CT or MRI. Perioperative antibiotic therapy for contaminated foreign body along with surgical removal of foreign body is the mainstay of management.

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Indian Journal of Clinical Practice, Vol. 31, No. 4, September 2020

Isolated Thalamic Involvement in a Case of Wernicke's Encephalopathy: An Atypical Presentation

CJ SELVAKUMAR*, ANIRBAN LAHA†, VELUSAMY SADEESHKUMAR*, N SHOBANA‡

ABSTRACT

We report the clinical and radiological profile of a case of Wernicke's encephalopathy with isolated thalamic involvement. Our patient, a 40-year-old male, alcoholic, was admitted in a drowsy state. There was no history of convulsions or trauma. On examination, Glasgow Coma Score (GCS) was E3V1M4, fundi were normal, reflexes were normal, meningeal signs absent. Routine investigations, computed tomography (CT) of brain were normal. A provisional diagnosis of Wernicke's encephalopathy was considered. Parenteral thiamine supplementation was given, following which patient's sensorium improved. Subsequently, features of impaired short-term memory, vertical gaze paresis, slow saccades, broken pursuits, scanning speech, intention tremor, ataxia and impaired tandem gait became evident. Magnetic resonance imaging (MRI) brain showed T2/FLAIR hyperintensities in bilateral thalamus, without diffusion restriction and without any mammillary body, periaqueductal, midbrain or cerebellar lesions. The highlight of this case is the clinical presentation of classic Wernicke's encephalopathy, caused by putative thalamic lesion only.

Keywords: Wernicke's encephalopathy, thalamus, ataxia

Wernicke's encephalopathy, described by Carl Wernicke in 1881, is characterized by ophthalmoparesis, nystagmus, ataxia and an apathetic – confusional state. It can present acutely or subacutely, and its pathogenesis is linked to thiamine deficiency. Chronic alcoholics and/or chronic malnourished patients are the at risk population. Lesions in Wernicke's encephalopathy involve periaqueductal regions, tectal plates, medial thalami and bilateral mammillary bodies. The patient in this case presented with typical features of Wernicke's encephalopathy but the lesion was limited to bilateral thalamus only, without involving other areas, the unique feature in this case. A high index of suspicion is essential as prompt treatment can favorably alter the outcome and prognosis.[1]

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CASE HISTORY

The patient, a 40-year-old gentleman, goldsmith by profession and a chronic alcoholic, was admitted in a drowsy state. He could be aroused by stimuli, but he was apathetic, and no effective communication or rapport could be established. There was no history of convulsion, trauma or headache. On examination, his pupillary and deep tendon reflexes were normal, plantar response was flexor bilaterally. Meningeal signs were absent. Patient's initial blood investigations (blood counts, biochemistry) and computed tomography (CT) scan of brain (Fig. 1) were normal. A provisional diagnosis of Wernicke's encephalopathy was made. Parenteral thiamine supplementation was started and gradually patient's alertness improved. Review examination revealed short-term memory impairment, impaired insight and judgment and perseverations in higher mental function assessment. Cranial nerve examination showed vertical gaze palsy with slow saccades and broken pursuits and gaze evoked nystagmus. Motor and sensory system examinations were normal. There was intention tremor, past pointing, significant truncal and stance ataxia with impaired tandem gait. Heel-shin test was positive. No extrapyramidal or autonomic findings were evident.

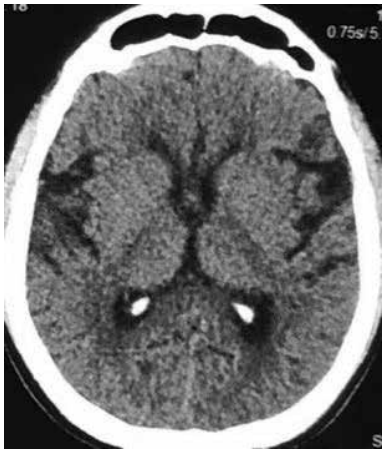

Figure 1. CT scan of brain showing normal brain morphology.

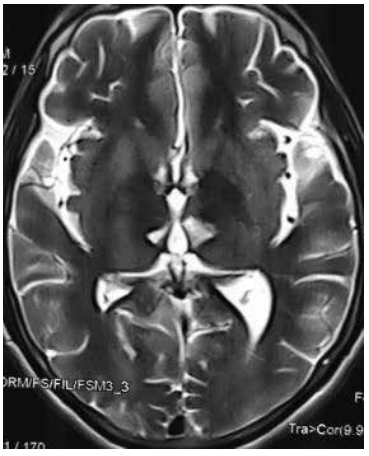

Figure 2. MRI brain (Axial T2 sequence) showing hyperintense signal change in bilateral thalamus.

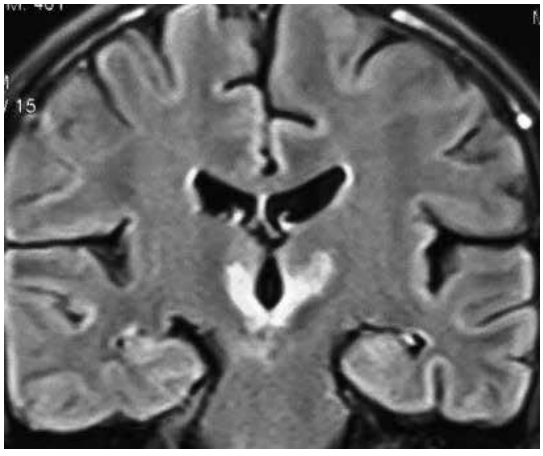

Figure 3. MRI brain (Coronal FLAIR sequence) showing hyperintense signal in bilateral thalamus.

Routine blood investigations – blood counts showed leukocytosis with left shift, with normal hemoglobin, red blood cell (RBC) and platelet indices; renal and liver function tests were within normal ranges. Viral markers were negative. Cerebrospinal fluid (CSF) study showed a cell count of 6 cells (lymphocytes), protein of 51 mg/dL and sugar of 77 mg/dL. CT scan of brain was normal. Magnetic resonance imaging (MRI) brain (Figs. 2 and 3) showed T2/fluid-attenuated inversion recovery (FLAIR) hyperintensity in bilateral thalamus, without any diffusion restriction or blooming. There was no abnormality of external capsule, lentiform nucleus, internal capsule, caudate nucleus. Midbrain, periaqueductal region, pons, medulla and cerebellum were normal.

Treatment with injection thiamine 500 mg IV followed by 100 mg TDS was given along with methylcobalamin, folic acid and multivitamins, IV antibiotics, IV fluids and another supportive treatment. Limb physiotherapy and balance exercises were started. Patient started walking with support and his overall general condition improved, although some residual gaze paresis and ataxia persisted.

DISCUSSION

The classic triad of Wernicke's encephalopathy includes confusion, ophthalmoparesis and ataxia. However, presence of all three features occurs in only about 16% of cases. In this case, all the three features were present. The population at risk is commonly chronic alcoholics, but other conditions have also been recognized, viz. hyperemesis gravidarum, systemic malignancy, gastrointestinal surgery (e.g., bariatric surgery), hemodialysis or peritoneal dialysis, prolonged IV feeding, refeeding after prolonged fasting or starvation, anorexia nervosa or dieting, acquired immunodeficiency syndrome (AIDS).[2]

The areas affected commonly include the periaqueductal regions, tectal plates, medial thalami and bilateral mammillary bodies. Other areas, including cerebellar vermis, pons, medulla, dentate nuclei, cranial nerve nuclei and basal ganglia are sometimes affected. MRI of brain is a sensitive investigative tool to pick up these lesions.[3] Interestingly in our patient although the clinical presentation was of classic Wernicke's encephalopathy, there was radiological evidence of only thalamic involvement.

The clinical and anatomical correlation reveals a central role of thalamus in the causation of the symptom complex.

Paramedian thalamic lesions are characterized by somnolence, apathy or transient coma, behavioral changes (confusion, disorientation, agitation, manic delirium, lack of initiative, apathy), recent memory loss (with anterograde and retrograde components), and, in some cases, abnormalities of vertical gaze. The cognitive and behavioral component is due to bilateral dorsomedial nucleus of thalamus involvement and the vertical gaze impairment in medial thalamic lesions is possibly due to interruption of supranuclear fibers traversing the medial thalamus en route to the pre-tectal and pre-rubral areas.[4,5]

Anterolateral thalamic lesions also lead to a neuropsychological disorder characterized by apathy and verbal perseveration, anterograde memory loss, facial paresis for emotional expression. They cause language disturbance (dominant hemisphere

involvement) and inattention (nondominant hemisphere involvement). Bilateral lesions may cause akinesia, amnesia and attention disturbance. Structures involved are anterior nucleus of thalamus, intralaminar nuclei (mainly the centromedian nucleus) and the mammillothalamic tract.[6]

Ventrolateral thalamic lesions cause hemiataxia, sensory loss and paroxysmal pain on the contralateral side of the body (posterior lesions), and disequilibrium (thalamic astasia), delayed tremor and axial supportive movement impairment (anterior lesions). There can also be choreoathetoid movements and athetoid postures (thalamic hand). Structures involved are ventral lateral nucleus, ventral posterior nucleus and the subthalamic region. In cases of hemiataxia-hypesthesia syndrome, lesions of ventral posterior nucleus and ventral lateral nucleus are found.[7]

The interest in this case was the classic clinical presentation of Wernicke's encephalopathy but with imaging evidence of only bilateral thalamic hyperintensities with normal appearance of midbrain, tectal plates, periaqueductal region and cerebellum.

The close differential diagnosis considered in this case was artery of Percheron infarct, but there was no diffusion restriction in the involved areas, thus it was unlikely. Other differentials in patients with bilateral thalamic lesions include metabolic causes (extrapontine myelinolysis, Fabry's disease, Wilson's disease), viral encephalitis (West Nile virus, Japanese encephalitis, Eastern equine encephalitis and rabies).[8]

CONCLUSION

Wernicke's encephalopathy is a treatable and reversible condition that is much under diagnosed and often missed. The classic clinical triad of confusion, ataxia, ophthalmoparesis may not be present always and altered sensorium is often the sole presenting symptom. High clinical suspicion should be kept in cases of at risk population, e.g., chronic alcoholics and nonalcoholic chronic malnourished states.

The thalamus has a central role in the clinical picture and interplays with other pathognomonic areas in disease causation. In some cases, the thalamus can be the only area affected. Prompt recognition and appropriate treatment with thiamine are the cornerstone for a favorable disease outcome.

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Do COVID-19 Antibodies Last 4 Months?

Antibodies to SARS-CoV-2 infection lasted for at least 4 months following initial infection, revealed a large serosurvey in Iceland.

Almost all people who tested positive for SARS-CoV-2 through quantitative PCR (qPCR) tests also tested positive with two pan-immunoglobulin (pan-Ig) SARS-CoV-2 antibody assays and continued to be seropositive after 120 days. The antibody titers by the two assays increased during 2 months after diagnosis, and did not exhibit any further decline over the last 2 months, reported the authors in the *New England Journal of Medicine*. Whether the antibodies were adequate to prevent reinfection was not addressed in the study… (*Medpage Today*)

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Indian Journal of Clinical Practice, Vol. 31, No. 4, September 2020

Transformation of Mature Teratoma into Adenocarcinoma in an 18-year-old Boy

MUKUR DIPI RAY*, AMAR RANJAN†, SACHIDANANDJEE BHARTI‡

ABSTRACT

An 18-year-old male presenting with testicular mass underwent orcheidectomy. On histopathological examination, mixed germ cell tumor was diagnosed. Tumor markers (alpha-fetoprotein [AFP] and beta-human chorionic gonadotropin [β-hCG]). were raised. Three cycles of chemotherapy with BEP regimen (bleomycin, etoposide and cisplatin) followed by radiotherapy of 51.2 Grays at 27 fractions was given. Post-chemotherapy, physical examination revealed a mass in epigastrium; supported by computerized tomography (CT), retroperitoneal lymph node dissection was done. The mass turned out to be adenocarcinoma. This study proposes the presence of malignancy component in mature teratoma.

Keywords: Germ cell tumor, mature teratoma, adenocarcinoma

Testicular cancers account for 1% of all malignancies in males, with the age group being 15-35 years.[1] Approximately, 95% of malignant tumors arising in the testis are germ-cell tumors (GCTs). GCT also occasionally arise in extragonadal primary sites, and their management follows that of testicular GCTs. More than 90% of patients with newly diagnosed GCTs are cured.[2,3] Two most challenging aspects faced by a surgeon are the growing teratoma syndrome and malignant transformation of a mature component of teratoma. The present report shows synchronous presentation of mature teratoma with adenocarcinoma infiltrating duodenum.

CASE REPORT

An 18-year-old young male presented with right-sided testicular swelling for 1 year. Incision biopsy revealed immature teratoma. Histopathological examination (HPE) of orchidectomy specimen revealed mixed GCT with yolk sac, trophoblastic and teratomatous components. The diagnosis was supported by tumor markers (alpha-fetoprotein [AFP] and beta-human chorionic gonadotropin [β-hCG]). Patient received 3 cycles of chemotherapy with BEP regimen (bleomycin, etoposide and cisplatin) followed by radiotherapy of 51.2 Grays at 27 fractions. After therapy, tumor markers were normalized, lactate dehydrogenase (LDH) remained marginally raised.

Post-chemotherapy, physical examination of abdomen revealed a mass of size approximately 10 cm in diameter in the epigastrium. Contrast-enhanced computerized tomography (CECT) scan of abdomen showed a 4 cm conglomerate mass in the aorto-caval location from lumbar vertebral level 2-4. Inferior vena cava (IVC) was compressed by the mass and 3rd part of duodenum was displaced (Fig. 1). In view of normalized tumor

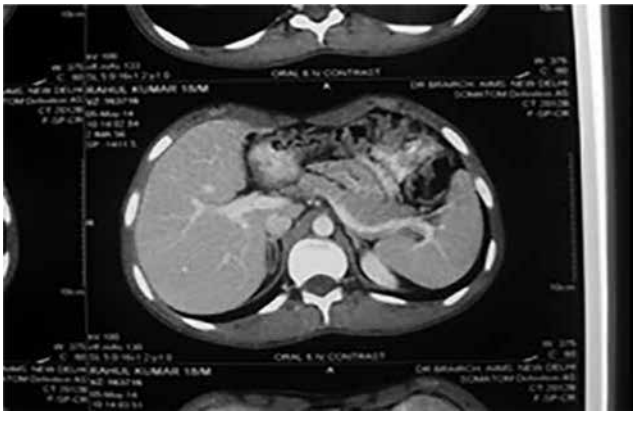

Figure 1. CT scan of upper abdomen showing a 4 cm conglomerate mass compressing IVC, displacing 3rd part of duodenum abutting abdominal aorta.

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markers, nonseminomatous germ cell tumors (NSGCT) histology and the residual lymph node mass in the retroperitoneum, retroperitoneal lymph node dissection (RPLND) was done.

Intraoperatively, a mass 6 cm in longest dimension was found in the aorto-caval junction. IVC and aorta were densely adhered to the mass, but could be separated. Duodenum was infiltrated completely from serosa to mucosa at the junction of second and third part, and an intraluminal proliferative growth was observed. All other solid organs were normal. En bloc resection of mass with the involved duodenum was done. Bowel continuity was achieved by duodenoduodenostomy. Retroperitoneal dissection was completed. Right side scrotectomy with inguinal lymph node dissection was done because of the previous scrotal violation at the time of incisional biopsy.

HPE of the resected mass revealed dysplastic glandular structures lined by pleomorphic cells infiltrating duodenal wall in the sections taken from the part of the mass in the duodenum, suggesting adenocarcinoma in a mature teratoma. Sections from other parts of the mass showed mature components of all three germ layers e.g., colonic epithelium, smooth muscle, adipose tissue, cartilage and focal squamous epithelium (Fig. 2 a and b).

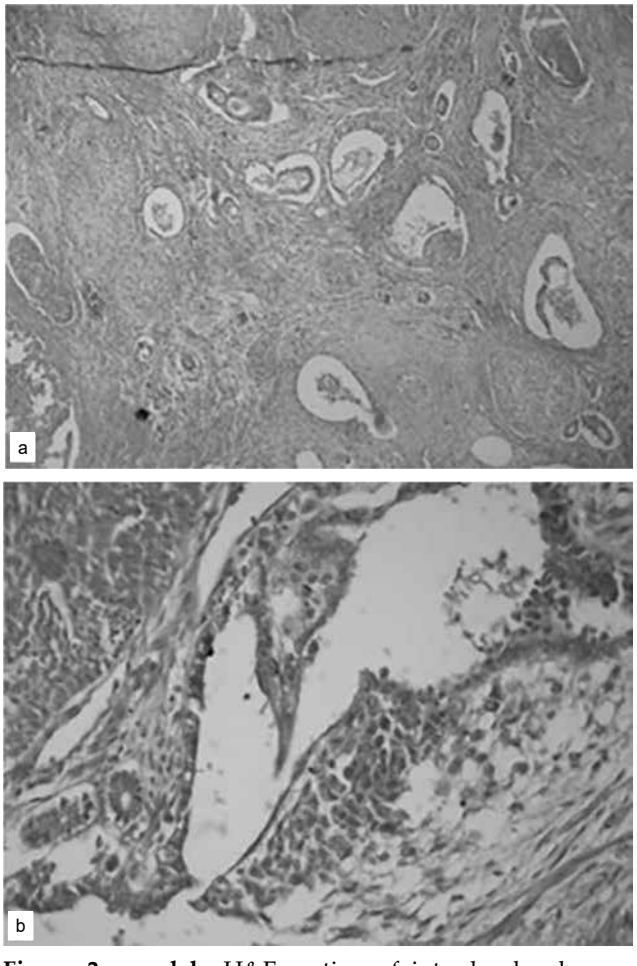

Figure 2 a and b. H&E section of intraduodenal mass showing dysplastic glandular structures lined by pleomorphic cells, 5X and 40X.

After surgery, patient is only on supportive therapy and is on follow-up regularly without any complication approximately 4 months after the second surgery.

DISCUSSION

Development of an invasive malignancy in mature teratoma is rare. Limited studies are available on this topic. A teratoma may transform in any form of malignancy. It does not respond to cisplatin base therapy. Surgical resection remains the mainstay of therapy.[4-6] But in our case after BEP regimen, patient is better till date.

Comiter et al (1998) studied 21 patients diagnosed with teratoma with malignant transformation during 7 years period. These were usually metastatic at presentation, more aggressive and had high recurrence rate. Mediastinal one had the worst prognosis.[4]

Malagón et al (2007) studied 46 patients with GCT transforming into sarcoma involving either primary sites or their metastases. These portend aggressive behavior and behave like an independent tumor.[5]

Motzer et al (1998) studied 46 patients with GCT, transforming into different malignancies. Sarcoma was the commonest. Others were adenocarcinoma, neuroectodermal tumor, leukemia, etc. The associated chromosomal abnormality was i(12p).[6]

Game et al in 2001 reported two cases of mature teratoma arising 3 and 20 years after the initial resection, occurring after macro- or microscopically incomplete resection of a mature teratoma.[7] Murphy et al in 1998 reported a 54-year-old male patient who was found to have adenocarcinoma arising within a mature teratomatous retroperitoneal metastasis 15 years after treatment of a NSGCT. The tumor was successfully excised and he remained without evidence of disease.[8]

Management of GCT is well-established. In cases of NSGCT, all the patients with stage IIB onwards will undergo chemotherapy with BEP regimen followed by imaging and tumor marker assessment. If the markers are normalized and imaging does not show any mass, no further treatment is required.[9]

If the CT shows any residual mass in the retroperitoneum or mediastinum, retroperitoneal lymph node dissection is

advised. Further treatment is planned as per histopathology report, which can be divided into 3 categories. One is only necrosis, which is present in up to 50% of patients second possibility is the presence of viable germ cell element (15%) and last situation is the possibility of teratoma component (35%).[10] The matured cells in the teratoma do not respond to the chemotherapeutic agents and they present as residual mass.

This study concludes that there is presence of invasive malignancy component in mature teratoma.

CONCLUSION

This study concludes that there is presence of invasive malignancy component in mature teratoma.

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Men and Women have Different Immune Responses to COVID-19

According to a small lab study, men and women seem to have different immune responses to COVID-19, which might explain some of their differing clinical courses.

Among patients with moderate COVID-19, men experiencing deterioration were older and had a higher body mass index (BMI) compared to men who were stable. On the contrary, both age and BMI levels were found to be comparable among women who deteriorated and those who were stable, reported researchers in *Nature*. Additionally, men with COVID-19 had higher plasma levels of innate immune cytokines, including interleukin (IL)-8 and IL-18. Women of all ages reported more robust T-cell activation compared to men. Among women, CD8 T cells were significantly higher compared to healthy volunteers, while the same was not evident among men… (*Medpage Today*)

BP Treatment Decreases CVD Risks, Even in Patients with Normal Levels

The treatment of systolic BP, even among those without evidence of cardiovascular disease, seems to decrease the risk of a composite of cardiovascular events, suggests new research presented at the European Society of Cardiology virtual meeting.

Kazem Rahimi, Deputy Director of the George Institute for Global Health and leader of the Healthcare Innovation and Evaluation Program at the University of Oxford, UK, stated that for every 5 mmHg decrease in systolic BP, an 11% RR reduction in the risk of experiencing the composite cardiovascular event endpoint (HR 0.89, 95% CI 0.86-0.920) was noted among individuals who did not have cardiovascular disease at baseline. Among patients with cardiovascular disease, for every 5 mmHg decrease in BP, there was a 9% reduction in the risk of an event (HR 0.91, 95% CI 0.89-0.94)… (*Medpage Today*)

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Tubercular Osteomyelitis of Talus in a Child: A Case Report and Review of Literature

RITESH RUNU*, MANTU JAIN†, VIDYA SAGAR‡, ARNAB SINHA‡, SAURAV KUMAR‡, SANTOSH KUMAR#

ABSTRACT

Introduction: Talar tuberculosis is very rare presentation of osteoarticular tuberculosis. Affection of foot is less than 10% in osteoarticular tuberculosis. Presentation of this disease in peripheral bones is highly unusual posing diagnostic dilemma and missed diagnosis. Delayed diagnosis may lead to complications. **Case report:** A 19-month-old male child presented with painful swelling over left foot and inability to bear weight. Hemogram was inconclusive. Radiograph showed lytic lesion in talus with cortical breach in the superior cortex. Aspiration biopsy was inconclusive and open curettage was done under anesthesia. Culture reports were negative but histopathological examination proved tuberculosis. Patient was given antitubercular therapy for 9 months and improved. **Conclusion:** Tuberculosis can affect any part of skeleton and high level of suspicion is essential. Culture negative lesion should be investigated and histopathological examination is essential for any lytic or infective lesion.

Keywords: Tuberculosis, talus, osteomyelitis, osteolytic

Tubercular talar osteomyelitis is an uncommon entity in children. Although tuberculosis of foot is well reported but talar tuberculosis is rare.[1,2] Involvement of talus due to subacute hematogenous osteomyelitis in children has been reported by several authors.[3-8] But, tubercular involvement of talus in children less than 2 years is rare.[1,2,9-17] Moreover, the mimicking radiological features with aneurysmal bone cyst, giant cell tumor and other infections poses diagnostic dilemma.[18-20] Here, we report a rare case of tubercular talar osteomyelitis in a 19-month-old male child who presented with pain and inability to bear weight on left lower limb.

CASE REPORT

A 19-month-old baby presented to our OPD with pain and intermittent low-grade fever for 5 months. Repeated consultation was done for fever with poor response. Limp was not noticed earlier, since child started walking at 14 months and repeated falls were taken as normal. The child had no history of cough, night sweating, loss of weight and appetite. Birth history and perinatal history were insignificant. Immunization schedule was followed as per guidelines including BCG vaccination at birth.

On examination, the general condition was fine. Vitals were stable and child was afebrile. On examination of left foot, it was swollen, tender and warm below the medial malleolus (Fig. 1). There was a boggy swelling over the talonavicular area medially. Ankle range of motion was normal. Foot pronation and supination was restricted. Distal neurovascular assessment was unremarkable. On investigation, hemoglobin (Hb) - 9.90 g/dL, total leukocyte count (TLC) - 14,680/mm^3, differential leukocyte count (DLC) showed neutrophils - 30%, lymphocytes = 56%, blood urea - 7.3 mg/dL, serum creatinine - 0.6%, erythrocyte sedimentation rate (ESR) - 55 mm and C-reactive protein (CRP) titer was raised. Test for viral markers was unreactive. X-ray showed osteolytic lesion in talus with breach in dorsal cortex (Fig. 2). On needle aspiration from talus, we found sanguineous fluid. It was sent for culture sensitivity, which was found sterile. On histopathological examination, only blood cell was found. The patient was kept on below knee pop slab, antibiotics and analgesics with no improvement.

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After a week, the patient was operated with differential diagnosis of chronic osteomyelitis of talus and aneurysmal bone cyst. Through anteromedial incision along tibialis anterior, the talus was approached. Talonavicular joint was exposed to confirm the talus. The talus was drilled over the neck proximal to talonavicular joint and it was thoroughly curetted. Material obtained was sent for Gram staining and Ziehl-Neelsen (ZN) staining, aerobic culture and sensitivity and histopathological examination. Once the normal endosteum was found then the wound was thoroughly lavaged and closure done. Postoperatively, the patient was kept on intravenous antibiotics and below knee plaster-of-Paris (POP) cast in equinus. ZN staining was positive for acid-fast bacilli. The culture and sensitivity report showed no growth, after 10 days; histopathological report confirmed tuberculosis. At 12th day, the stitches were removed and antitubercular therapy was started. After consultation with pediatric department. The patient was discharged on below knee POP cast in equinus. Total 9 months of antitubercular therapy was given with 3 months each for intensive, continuation and maintenance phase. At 1-year follow-up, the patient is doing well with complete healing of the lesion.

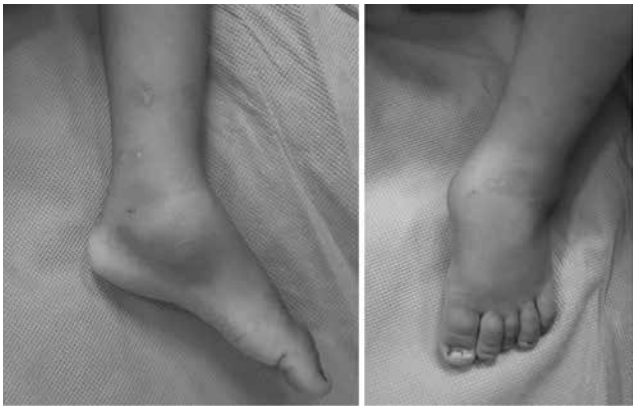

Figure 1. Clinical picture of the patient showing swelling and signs of inflammation.

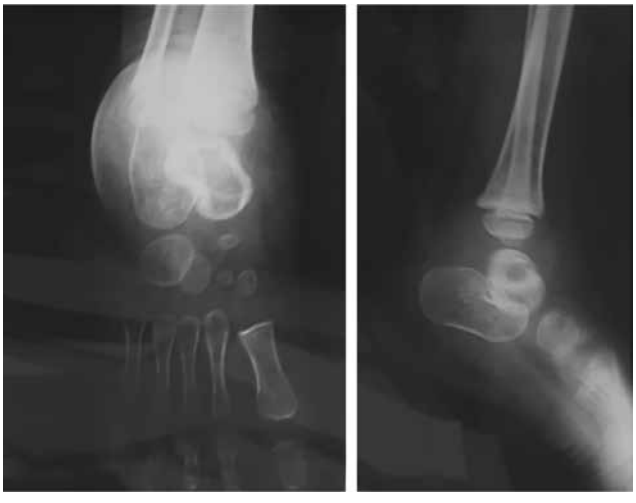

Figure 2. X-ray anteroposterior and lateral view showing a lytic lesion involving the talus.

DISCUSSION

Tuberculous involvement of skeleton is 1-3% of extrapulmonary tuberculosis.[1] Involvement of foot among osteoarticular tuberculosis is less than 10%.[1] Among all bones of foot, osteomyelitis of talus is rare.[1-8] Our search in electronic and print media revealed cases mostly about subacute hematogenous osteomyelitis of talus and foot bones.[3-8] Dhillon[1] and Mittal[2] have reported exclusively on tuberculosis of foot bones. Only one case of talar osteomyelitis out of 24 cases was reported by Dhillon et al[1] and none out of 44 cases in a series by Mittal et al.[2] Isolated case reports on talus have been reported in recent years and are given chronologically in Table 1.[9-17] Our patient is the youngest case to be reported.

The diagnosis is usually difficult since presentation is vague and nonspecific.[4,7] Flexion at hip and knee with limb in external rotation may be present.[4] Swelling and redness in the foot may be delayed feature.[4] Location of swelling is variable. Verbeek[4] reported swelling on the lateral aspect while Ganaisan[5] reported swelling over the ankle area. We noticed swelling on the medial aspect of mid-foot. Constitutional symptoms are usually nil.[1,2,6,7] In our case, low-grade fever and inability to bear weight for 5 months was the only complaint.

Delayed diagnosis is usually due to lack of constitutional symptoms, poor localizing signs, low level of suspicion

Table 1. Isolated Cases of TB Talus as Reported in Chronological Order

Author	Year of reporting	Age of patient (years)
Anand et al[9]	2002	8
Teklali et al[10]	2003	20 months
Ebrahimzadeh et al[11]	2006	7
Mardanpour et al[12]	2010	52
Arora et al[13]	2014	45
Dahuja et al[14]	2014	14
Mohammad et al[15]	2015	42
Sekhon et al[16]	2015	14
Khan et al[17]	2016	5

and simulating radiological features.[1-8,18,19] Symptoms to admission was 5 months average (Dhillon[1]), 1 month (Ganaisan[5]), 2-12 weeks (Ezra[6]), 5 days to 4 weeks (Grattan-Smith[7]) and 1-5 months (Skevis[8]). In our case it was 5 months.

Hemogram shows signs of infection with raised ESR,[1,4-8] but CRP is rarely raised.[4,6] In our case, the ESR and CRP were raised along with lymphocytosis.

Conventional radiography is the primary tool for diagnosis. Phemister's triad of periarticular osteoporosis, marginal erosions and narrowing of joint space is usually seen in osteoarticular tuberculosis. But, this feature is not evident in foot bones always.[2] Mittal et al[2] observed five patterns of foot bone lesions in tuberculosis: cystic, rheumatoid, subperiosteal, kissing and spina ventosa. In our case, it was cystic type of lesion, which has central osteolytic lesion with no sequestrum and no periosteal reaction.

The lesion in foot usually mimics other conditions as well.[18-20] Aneurysmal bone cyst, giant cell tumors and infections of foot bones mimics cystic type of tuberculosis. Shirazi et al[20] noted aneurysmal bone cyst was as common as giant cell tumor of small bones of hand and feet. Infections and inflammatory simple cysts were equally prevalent in less than 10 years old children.[20] We found blood on aspiration from talus in our case. Hence, our differential diagnosis was aneurysmal bone cyst and chronic osteomyelitis.

Computed tomography (CT) scan, magnetic resonance scan and bone scan of foot is usually required to localize the lesion and to see the soft tissue condition.[1,2,4-7,18] Magnetic resonance imaging (MRI) shows changes consistent with chronic osteomyelitis.[5] Bone scan with gallium-67 (Ga-67) and technetium-99 (Tc-99) shows increased tracer uptake in the tarsal bones.[6,7] On getting negative report on aspiration cytology and culture sensitivity we directly opted for curettage exploration of the lesion as suggested by Dhillon et al.[1] The same has been done by other authors.[1,7,18,20] The culture report is usually negative since osteoarticular tuberculosis is a paucibacillary condition.[1,2,7] Open curettage and biopsy is usually required for diagnosis.[1,2,7,8,18-20]

Minimal pus and granulation tissue is found with evidence of necrotic bone and polymorphonuclear infiltrate.[7] As a rule, we send sample for culture in every case of suspected tumor and we do histopathological examination of every abscess.

Following the rule, we found granuloma in our case. Culture negative and lack of conclusive diagnosis can be curtailed by early biopsy. Delay in diagnosis may lead to complete destruction of bone and joints. Hence, early diagnosis is the priority.

CONCLUSION

Age is no bar for osteoarticular tuberculosis. Any osteolytic lesion in talus or foot bones should be investigated and high level of suspicion is essential to rule out tuberculosis. All the abscesses should be biopsied to prevent missed diagnosis. Early diagnosis and complete treatment of tuberculosis should be the aim.

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■■■■

Steroids Reduce Death Rates Among Critically Ill COVID-19 Patients, Says Study

London: Treating critically ill COVID-19 patients with corticosteroids tends to reduce the risk of death by 20%, suggests an analysis of seven international trials.

The analysis included data from separate trials of low-dose hydrocortisone, dexamethasone and methylprednisolone. It was noted that steroids improve survival rates of COVID-19 patients who require intensive care in hospital. Researchers stated that this was equivalent to nearly 68% of the sickest COVID-19 patients surviving after treatment with corticosteroids, compared to about 60% surviving in the absence of corticosteroids. The WHO's clinical care lead, Janet Diaz, has also stated that the agency has updated its advice to include a "strong recommendation" for the use of steroids among patients with severe and critical COVID-19… (*ET Healthworld – Reuters*)

Novavax Coronavirus Vaccine Safe, Suggest Published Results

Early stage clinical trial results suggest that the COVID-19 vaccine candidate by Novavax is safe and evokes an immune response. The study results, published in *The New England Journal of Medicine*, had previously been announced in early August.

The vaccine or placebo was administered to 131 healthy adults in May in a randomized, placebo-controlled trial. In all, 83 individuals got the vaccine with adjuvant, an agent to boost the body's immune response. Twenty-five people got the vaccine without the booster and 23 were given the placebo. The trial participants also received a second injection 21 days following the first. The vaccine appeared to elicit an immune response and all the volunteers who got the vaccine developed neutralizing antibodies after the second dose… (*CNN*)

SSRI Use After Intracerebral Hemorrhage

While selective serotonin reuptake inhibitors (SSRIs) can effectively treat depression following intracerebral hemorrhage (ICH), they tend to heighten the risk for recurrent hemorrhagic stroke, especially in patients at high risk for repeat ICH, suggests new research.

Investigators followed 1,279 adults for a median of 4.5 years following primary ICH. During follow-up, 128 patients suffered recurrent ICH (annual rate, 4.2%) and 766 (60%) were diagnosed with depression. As per the multivariable analyses, SSRIs were found to be associated with higher odds of post-ICH depression remission (subhazard ratio [SHR], 1.53; 95% CI, 1.12-2.09; p = 0.009). SSRI use was found to be an independent risk factor for recurrent ICH (SHR, 1.31; 95% CI, 1.08-1.59; p = 0.006). The findings are published online in *JAMA Neurology*… (*Medscape*)

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Medtalks with Dr KK Aggarwal

CMAAO Coronavirus Facts and Myth Buster

Round Table Expert Zoom Meeting on "Will COVID-19 Surge Come Back Again?"

8th August, 2020 (11 am-12 noon)

Participants: Dr KK Aggarwal, Prof Mahesh Verma, Dr Suneela Garg, Dr Narottam Puri, Dr Alex Thomas, Dr Atul Kochhar, Dr Ashok Gupta, Dr JA Jayalal, Dr Jayakrishnan Alapet, Dr Anil Kumar, Mrs Upasana Arora, Dr KK Kalra, Ms Ira Gupta, Dr S Sharma

Key points from the discussion

- With unlock 3.0, the people have relaxed; winter is approaching, when a new wave is expected. We have seen that summer had no effect on the number of cases.
- There are 6 strains of the coronavirus: L strain (original strain in Wuhan), strains S, V, G, GR and GH. Strain G and its related strains GR and GH are the most common. In North America, the most widespread strain is GH, while in South America, we find the GR strain more frequently. In Asia, where the Wuhan L strain initially appeared, the spread of strains G, GH and GR is increasing. Globally, strains G, GH and GR are constantly increasing. Strain S can be found in some restricted areas in the US and Spain. The L and V strains are gradually disappearing (*Science Daily*).
- Up to 30% of additions/substitution can occur in the same strain. If the virus undergoes 70% mutation, it becomes a new virus.
- When we define a surge, we should consider a few points: Is it a new mutation? Is it a new strain? How does a virus behaves? Is it a superspreader?
- The surge can be due to a new virus, same virus but mutated and same virus but local spread (superspreader, Dharavi).
- If surge is due to a new strain, the mortality may be different and higher initially. If it is a surge in existing strain, then spread will be high, but mortality will be low.
- Pandemics are won by communities.
- In Delhi and Mumbai, the surge was in downtown, as social distancing and/or face masks were not adhered to.
- Reverse transcription polymerase chain reaction (RT-PCR) detects viral antigens (E, S, M, ORF, NS, RdRp); if E antigen is negative, no corona. All labs do not test for all antigens. If the kits test for multiple antigens, the sensitivity of the test is higher. This will reduce the chances of false negative result.
- Cohort pooled cycle threshold (Ct) value high - this means that the virus is getting attenuated. Ct value cannot be the only basis of the report (Indian Council of Medical Research [ICMR]), it has to be combined with clinical interpretation; Ct value can change according to the kit used; it may be operator-dependent. The cut-off value must also be mentioned. It is important for clinicians to know the viral load.
- Family clusters may have varied symptoms. But people are not coming forward.
- Prevention is very important, but it is not 100% preventable; our concern is to also reduce the mortality. All efforts today are towards reducing the infection and less effort in reducing the mortality.
- Western models will not work in India. We should learn from each other about things that are unique to India.
- It is important to identify Day 1. CT scan can become positive on Day 3. If RT-PCR report is not available or it may be false-positive, then CT becomes important. Don't wait for Day 5, as complications may set in by this time. One must act on Day 3.

Minutes of Virtual Meeting of CMAAO NMAs on "Asian Countries Update – Part 2"

8th August 2020, Saturday (9.30 am-10.30 am)

Participants: Member NMAs

Dr KK Aggarwal, President-CMAAO; Dr Yeh Woei Chong, Singapore Chair-CMAAO; Prof Ashraf Nizami, Pakistan - First Vice President, CMAAO; Dr N Ganabaskaran, President-Malaysian Medical Association; Dr Marthanda Pillai, Member-World Medical Council; Dr Alvin Yee-Shing Chan, Hong Kong; Dr Marie Uzawa Urabe, Japan; Dr Ashraf Nizami,

Pakistan; Dr Sajjad Qaisar, Pakistan; Dr Md Jamaluddin Chowdhury, Bangladesh; Dr Prakash Budhathoky, Nepal; Dr Lochan Karki, Nepal

Invitees: Dr Russell D'Souza, UNESCO Chair in Bioethics, Australia; Dr Zion Hagay, Israel Medical Association; Dr S Sharma, Editor-IJCP Group

Key points from the discussion

- The correct interpretation of RT-PCR test, done with 2 antigens, same reagent and same lab results is important.
- Rising Ct value means that the viral load is reducing.
- After 9 days, the virus is detectable but does not replicate and is nonculturable.
- Coronavirus disease 2019 (COVID-19) is an "acute immunoinflammatory manageable viral illness with post viral phase".
- Singapore is reaching the tail end of the epidemic. Swabbing of all migrant workers (3,30,000) has been completed and large numbers of them have returned to work. Community cases remain 1-2 per day.
- Malaysia is concerned about the issue of illegal immigrants.
- In Indonesia, testing is inadequate; they are using luminosity to find out the situation, i.e., they send a satellite at night and measure the light pattern all over the country and compare with base data from previous years and estimate the amount of COVID cases from satellite images.
- In Bangladesh, tests are limited (12-13,000/day), 4-25% are positive, mostly the young have the infection, people are losing interest.
- In Pakistan, people are not following SOPs to prevent the infection; they don't use mask or observe social distancing.
- In Nepal, when the infection first came in, the cases were asymptomatic; after lockdown relaxed, the cases have again started to increase. Most cases now are symptomatic. This may be due to a new mutation of the virus.
- Prevent the infection as much as you can; if you can't, then manage it. If positivity rate is >10%, then strict precautions need to be taken; if it is less than 5%, then let the infection happen. If 25% of population is infected, then the first wave is likely to be over. This is herd immunity for the first wave.
- There are 6 strains of the coronavirus: L strain (original strain in Wuhan), strains S, V, G, GR and GH.
- Multifaceted approach to reduce the infection: state, society and the individual.
- RT-PCR detects viral antigens (E, S, M, ORF 1a, 1b, NS, RdRp); if E antigen is negative, no corona. If the kits test for multiple antigens, the sensitivity of the test is higher. For doctors, a policy recommendation can be made that minimum 2-3 antigen tests must be done; this will reduce the chances of false-negative result.
- After 10 days, the virus is nonreplicable, so test is not required after 10 days. The person can move out and after 14 days, can resume work.
- The government of Bangladesh is considering a new order regarding duty hours of doctors. Earlier, 7 days' work and 14 days' quarantine (7 days at home) and then resume work. Now the Bangladesh government has changed this to 14 days work and 14 days quarantine (no home stay).
- The participating NMAs were of the opinion that working for 14 days straight is not a very sensible recommendation as fatigue sets in. Not allowing doctors to go home to their families may result in mental health problems. Working hours should also be reduced to reduce viral load. However, this could lead to shortage of manpower.
- A resolution was passed to be sent to Dr Md Jamaluddin Chowdhury, representing the Bangladesh Medical Association for discussion with the government. *"In a CMAAO meeting today, 8th of August 2020, it was resolved unanimously that COVID-19 duties for medical staff should not exceed more than 7 days at a stretch and the daily shift should not exceed 8 hours."*
- Dr Alvin raised the issue of resident doctors' strike in South Korea, who are protesting the government's decision to increase the number of medical students in the country to meet the shortage. CMAAO would try to reach out to South Korea to see if they need any kind of assistance.

CMAAO Formula

- **Death in symptomatic cases:** less than 1% (with best of care). Therefore, deaths × 100 = expected number of symptomatic cases.
- **Cases after 7 days:** Cases today × 2 (based on doubling time 7; this will vary from country to country).
- **Cases expected in the community:** Get the number of deaths occurring in a 5-day period;

estimate the number of infections required to generate these deaths based on the country or area case fatality rate; compare that to the number of new cases actually detected in the 5-day period. This can give an estimate of the total number of cases (confirmed or unconfirmed).

- **Lockdown effect:** Reduction in number of cases after average incubation period (5 days).
- **Lockdown effect in reduction in deaths:** Reduction in number of deaths on Day 14 (average time to death of that country).
- **Requirement of ventilators on Day 9:** 1-3% of number of new cases detected.
- **Requirement of future oxygen on Day 7:** 10% of total cases detected today.
- **Requirement of ventilators:** 1-3% of number of cases admitted 7-9 days back.
- **Requirement of oxygen beds today:** 10% of total cases admitted 7 days back.
- **Case fatality rate:** Number of total deaths as on date/number of total RT-PCR positive cases as on today.
- **Infection fatality rate:** Number of total deaths as on date/number of total calculated cases as on today.
- **Number of people which can be managed at home care:** 90% of number of cases today.
- **Number of reported deaths:** Number of confirmed deaths × 2.
- **Number of asymptomatic cases:** For 6 symptomatic cases, 200 asymptomatic cases.
- **Number of unreported or untested cases =** Number of reported cases × 10-30 depending on the country.

Update on COVID-19: IMA-CMAAO Webinar on "Understanding Coronavirus Differently"

15th August, 2020 (4-4.30 pm)

Participants: Dr KK Aggarwal, President-CMAAO; Dr RV Asokan, Hony Secretary General-IMA; Dr Ramesh K Datta, Hony Finance Secretary-IMA; Dr S Sharma, Editor-IJCP Group

Faculty: Dr KK Aggarwal, Padma Shri Awardee, President-CMAAO & HCFI

Key points from the discussion

- The new coronavirus behaves in 6 different ways: Viral, bacterial, HIV-like, it causes immuno-inflammation, thromboinflammation and cytokine storm.
- This virus causes immune (antigen) triggered inflammation wherever angiotensin-converting enzyme 2 (ACE2) receptors are present. If there is pre-existing inflammation, it will flare up.
- This is a disease of the inflammation of the digestive and metabolic fires of the body.
- There are two types of fire or agni in the body: microbiome fire and my agni fire. The balance or imbalance between the two causes health and disease. This virus triggers and increases agni in the body, leading to disruption of the body's thermostat, resulting in low-grade fever.
- If baseline C-reactive protein (CRP) is <1, then no impact; if 1-3, then exacerbation of fire, and if more than 3, then there is high hyperinflammation leading to vasculitis, thrombus formation, neoangiogenesis and hypoxia.
- The route of entry is gastrointestinal (GI) or respiratory tract. The virus may be present in GI system much before it is seen in the respiratory system and even if not seen in the respiratory tract.
- Skin biopsy may also be positive for the virus (*Lancet*).
- If fragments of the antigen persist, the person may be a carrier; they may also cause recurrence of symptoms, reactivation of illness and trigger inflammation.
- There are 6 antigens in COVID-19 virus: E, S, N, ORF 1a, ORF 1b and RdRp antigen. The RT-PCR test assesses the antigens and not the virus.
- E antigen is a must; it is common for all coronaviruses. If negative, no corona.
- We do not know yet which antigen persists for more than 9 days. We must find out which of these antigens is infectious.
- When we say RT-PCR is positive, it is important to know which antigen is positive.
- True Nat tests RdRp; Singapore, at airports, is testing N, ORF and S.
- If we find out which part of the virus (antigen) is causing which inflammation, this could be a game changer.
- In patients with insulin resistance, where there is already low-grade inflammation, the trigger is faster and more significant.

Steroid and Diabetes

New guidance from the UK National Diabetes COVID-19 Response Group (August 2 in *Diabetic Medicine)*

- Address the triple insult of dexamethasone-induced impaired glucose metabolism, COVID-19-induced insulin resistance, and COVID-19 impaired insulin production.
- Randomised Evaluation of COVID-19 Therapy (RECOVERY) trial revealed that dexamethasone led to reduction in deaths in patients with COVID-19 on ventilators or receiving oxygen therapy. The dose used in the trial was 6 mg daily for 10 days, which is 5-6 times greater than the therapeutic glucocorticoid replacement dose.
- High glucocorticoid doses can result in exacerbation of hyperglycemia in those with established diabetes, can unmask undiagnosed diabetes, cause hyperglycemia or new-onset diabetes, and can also lead to hyperglycemic hyperosmolar state (HHS).
- The guidance recommends a target glucose of 108-180 mg/dL and further states that up to 216 mg/dL is acceptable.
- It recommends the use of once- or twice-daily NPH insulin for patients with glucose above 216, in certain cases with the addition of a long-acting analog.
- Patients already taking premixed insulin formulations can continue, while increasing the dose by 20-40%.
- Considering the risk of hypoglycemia associated with those formulations, many experts say that they would switch those patients to NPH during the time they're being given dexamethasone. (*Medscape Excerpts*)

Comments

- Steroid-induced high sugar is often post meals.
- Give repaglinide 1 mg or 2 mg sublingual before meals.
- Add 0.3 units insulin per kg in divided doses.
- In high-risk cases steroids may have to be started on Day 1 itself so adjust dose accordingly.
- In post-COVID illness, steroids may have to continue for weeks together like in any immunological illness.

Update on COVID-19: Minutes of Virtual Meeting of CMAAO NMAs on "Asian Countries Update – Part 2"

15th August, 2020 (Saturday, 9.30 am-10.30 am)

Participants: Member NMAs

Dr KK Aggarwal, President-CMAAO; Dr Yeh Woei Chong, Singapore Chair-CMAAO; Dr Alvin Yee-Shing Chan, Hong Kong; Dr Marie Uzawa Urabe, Japan; Dr Sajjad Qaisar, Pakistan; Dr Prakash Budhathoky, Nepal

Invitees: Dr Russell D'Souza, UNESCO Chair in Bioethics, Australia; Dr S Sharma, Editor-IJCP Group

Key points from the discussion

- The COVID-19 virus has 6 antigens: E, S, N, ORF 1a, ORF 1b and RdRp antigen. E antigen is common to coronaviruses; if negative, no corona. The rest 5 are specific to COVID-19.
- RT-PCR – antigen has been reported for up to 40 days. But, there is no data available as to how long any of these antigens last in the body.
- The RT-PCR tests the antigen; it does not detect the virus. If only one antigen is tested, the sensitivity is low. Testing for 2 or more antigens incurs higher cost.
- In cold, frozen foods, the virus can survive for much longer.
- The virus becomes nonreplicable inside the body after 9 days.
- We need to have studies to find out how long these antigens remain inside the body.
- The virus is present in skin. *The Lancet* has published a case report where RT-PCR was negative, but the skin biopsy samples from rash, were positive for the virus.
- COVID-19 causes immune hyper-reaction in the body. It is a multisystem disorder, especially in children and now, also in adults. Skin could also be involved.
- It is the duty of the treating doctor to decide after Day 14, whether his patient is infectious or not.
- The certificate stating simply positive/negative status has no value. The doctor should mention if the patient is infectious or not.
- For instance, a doctor should be able to give a certificate that the patient is noninfectious under following conditions: the patient demonstrates the presence of immunoglobulin G (IgG) antibodies with or without presence of antigens,

the patient is asymptomatic after 10 days without doing antigen test, the patient is positive for 2 weeks, his erythrocyte sedimentation rate (ESR) and CRP are normal.

- We should know which antigens are being tested. A person detected negative in one country may test positive in another country. This depends on the antigen/s being tested.
- It was suggested that a survey could be conducted in the member countries to find out which country is testing which antigen.
- In Singapore, chip machines check for N, ORF and S antigens at the airports.
- In Japan, the quarantine period has been reduced from 14 days to 10 days. It is a recommendation and not a law.
- Regarding the strike in South Korea, it is risky to issue a statement without knowing all facts.
- Melbourne has reached the peak; the cases are now coming down
- Masking and social distancing will only prevent the infection. So, prevent as long as you can and as much as you can.

CDC Updated Guidance does not Imply Immunity to Reinfection

People who are infected with COVID-19 do not necessarily have immunity to reinfection for 3 months, said CDC.

It is possible that people may continue to test positive for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) for up to 3 months following diagnosis and not transmit the infection to others. But, this does not imply that infection confers immunity for that period.

The confusion had emanated from an August 3 update to CDC's isolation guidance. The guidance stated the following:

"Who requires quarantine?

People who have been in close contact with someone who has COVID-19 - excluding people who have had COVID-19 within the past 3 months.

People who have tested positive for COVID-19 do not need to quarantine or get tested again for up to 3 months as long as they do not develop symptoms again. People who develop symptoms again within 3 months of their first bout of COVID-19 may need to be tested again if there is no other cause identified for their symptoms."

One may read these statements as suggesting that those who are recovering from COVID-19 would possibly be protected from reinfection for 3 months even with close exposure to infected people. Media reports took this as the agency is implying immunity.

However, a new statement from the CDC has condemned the media for misinterpreting its guidance. According to CDC, the guidance was about retesting, and not immunity.

The latest data indicate that retesting in the 3 months following initial infection is not required unless the person develops the symptoms of COVID-19 and the symptoms cannot be tied to another illness.

The CDC went on to update and state categorically that it is not known if someone can be re-infected with COVID-19.

According to the CDC, individuals who were previously infected with COVID-19 may continue to have low levels of virus in their body for up to 3 months, hence, the positive test results even if they recovered from the virus.

The CDC thus concluded that the duration of infection in the majority of patients is no more than 10 days following symptom onset, and no more than 20 days in those with severe illness or in severely immunocompromised individuals.

The agency also stated that there are no confirmed reports of reinfection within 3 months of initial infection.

The guidance recommends that if patients recovering from COVID-19 come in contact with a positive case and have new symptoms, they should isolate themselves, contact their healthcare provider and possibly undergo retesting.

All the people, including those recovering from the infection, should follow the recommended interventions, including social distancing, wearing a face mask in public and washing of hands.

The CDC restated that people testing positive for COVID-19 should isolate for at least 10 days following symptom onset and until 24 hours after the fever subsides without the use of antipyretic medications.

(*Source: Medpage Today*)

Delhi – About 29% Prevalence of COVID-19 Antibodies

Second Sero-survey Suggests 28% in City have Antibodies

- The previous serological survey conducted by the National Centre for Disease Control (NCDC)

among 21,387 individuals demonstrated that 22.86% of the people surveyed had been exposed to the novel coronavirus.

- The second serological survey, conducted in the first week of August across Delhi, has shown that 28.35% of the people surveyed have developed antibodies.
- Over 15,000 samples were obtained across 11 districts in the national capital to check for the spread of the virus.
- The data collated by researchers at Maulana Azad Medical College was submitted to Principal Health Secretary, Vikram Dev Dutt.
- The central district has reported the highest prevalence.
- Sampling taken: 25% less than 18 years, 50% ages 18-49 years and 25% over 50 years of age.
- Antibodies in males: 28.3%.
- Antibodies in females: 32.2%.
- Less than 18 years: antibodies in 34.7%.
- 18-49 years: antibodies in 28.5%.
- Over 50 years: antibodies in 31.2%.

Vaccine Nationalism

The wealthier countries that have more money are entering into pre-purchase deals with pharmaceutical companies to purchase a coronavirus vaccine once the trials prove to be successful. With several companies across the globe conducting research on a COVID-19 vaccine, the wealthier nations have already placed orders worth millions to obtain the first shots.

Cohort Isolation

Patients should be placed in a well-ventilated single-occupancy room with a closed door and a dedicated bathroom. If not possible, patients with confirmed COVID-19 can be accommodated together. Additionally, patients with confirmed COVID-19 infection should not be placed in a positive-pressure room. An airborne infection isolation room (AII; i.e., a single-patient, negative-pressure room) should be used for patients undergoing aerosol-generating procedures. (*Uptodate*)

Kidney a 'Bystander' in COVID-19

A study from Canada has shown that there is enhanced expression of ACE2 receptors in the kidneys of patients with diabetic nephropathy. This could possibly explain why these patients have an increased risk of COVID-19 and have severe outcomes. However, the SARS-CoV-2 virus directly infects the kidneys has not been proven so far. Kidney damage may be the by-product of COVID-19 impact elsewhere in the body. The new study was published as a journal pre-proof in the *Canadian Journal of Diabetes*. (*Medscape*)

SARS-CoV-2 Causes a Specific Dysfunction of the Kidney Proximal, Says Study Tubule

A study published in *Kidney International* suggests that SARS-CoV-2 leads to an early and specific dysfunction of the kidney proximal tubule (PT), which is marked by low-molecular-weight (LMW) proteinuria, neutral aminoaciduria and defective handling of uric acid and phosphate. ACE2 receptor for SARS-CoV-2 is known to be highly expressed in the PT cells.

In the study, around 67% had raised urinary levels of β2-microglobulin, 85% had a urinary protein-to-creatinine ratio (UPCR) of >0.2 g/g, and 98% reported having a urinary albumin-to-protein ratio (UAPR) <0.5.

Electrophoresis of urine samples from the patients showed multiple protein bands below 70 kDa (LMW proteinuria), which included the vitamin D-binding protein (DBP) and Clara cell secretory protein (CC16).

About 47% and 56% of the patients had hypouricemia and/or hypophosphatemia, respectively.

About 46% had defective tubular handling of uric acid (hypouricemia with inappropriate uricosuria; FE_{UA} >10%). Hypophosphatemia with inappropriate phosphaturia (FE_P >20%) was seen in 19%.

Around 46% of the patients had aminoaciduria, which was restricted to neutral amino acids.

PT dysfunction was shown to be independent of pre-existing comorbidities, glomerular proteinuria, nephrotoxic medications or viral load among the cohort.

Over a median follow-up of 44 days, 39% of patients needed invasive mechanical ventilation, 29% died, 22% developed acute kidney injury (AKI) and 4% required kidney replacement therapy. Hypouricemia with inappropriate uricosuria had an independent association with disease severity and with a significant increase in the risk of respiratory failure requiring invasive mechanical ventilation.

The study reveals that PT dysfunction develops in a subset of patients with COVID-19 and is marked by LMW proteinuria, hypophosphatemia and hypouricemia due to inappropriate urinary loss of phosphate and uric acid, and neutral aminoaciduria.

Hypouricemia was common and associated with poor outcome in patients with SARS.

Potential mechanisms that link PT dysfunction and respiratory failure may include loss of vital solutes, including uric acid, which may impact the defense against oxidative stress and respiratory function. (*DG Alerts*)

Reasons for Loss of Smell

ERS: Study of nose and throat reveals why people with COVID-19 may lose their sense of smell

Researchers who have been studying tissue removed from patients' noses during surgery believe that they may have identified the reason for loss of sense of smell among COVID-19 patients, even when they have no other symptoms.

Investigators noted very high levels of ACE2 only in the area of the nose responsible for smelling. This enzyme is believed to be the portal of entry for the coronavirus to get into the cells of the body and cause an infection.

Findings, published in the *European Respiratory Journal*, offer clues to the high infectivity of COVID-19 and suggest that targeting this particular part of the body could help determine more effective treatments.

While other respiratory viruses generally cause loss of sense of smell by obstructing the airflow due to swelling of the nasal passages, this virus sometimes causes loss of smell when there are no other nasal symptoms.

Investigators used tissue samples from the back of the nose of 23 patients that were removed during endoscopic surgical procedures for conditions such as tumors or chronic rhinosinusitis. Biopsies from the trachea of 7 patients were also studied. None of the patients had been diagnosed with COVID-19.

Fluorescent dyes were used on the tissue samples to detect and visualize the presence of ACE2 under a microscope. Investigators compared the levels of ACE2 in different cell types and parts of the nose and upper airway.

They found the most ACE2 on the lining cells of the olfactory epithelium, the area at the back of the nose where smells are detected.

The levels of ACE2 in these cells was found to be 200- to 700-times higher than other tissue in the nose and trachea. High levels were observed in all the samples of olfactory epithelium, irrespective of the condition the patient had been treated for. ACE2 was not detected on olfactory neurons.

The levels of ACE2 were found to be the highest in the part of the nose that is responsible for smell. The results thus suggest that this area of the nose could be the part where the coronavirus is entering the body.

A virus can easily reach the olfactory epithelium, and the very high levels of ACE2 in this part might explain why it's so easy to catch COVID-19.

Source: https://healthcare-in-europe.com/en/news/study-reveals-why-people-with-covid-19-may-lose-their-sense-of-smell.html

Minutes of Virtual Meeting of CMAAO NMAs on "Asian Countries Update – Formula of Six"

22nd August, 2020 (Saturday, 9.30 am-10.30 am)

Participants: Member NMAs

Dr KK Aggarwal, President-CMAAO; Dr Yeh Woei Chong, Singapore Chair-CMAAO; Dr Marthanda Pillai, Member-World Medical Council; Dr Alvin Yee-Shing Chan, Hong Kong; Dr Marie Uzawa Urabe, Japan; Dr Md Jamaluddin Chowdhury, Bangladesh; Dr Prakash Budhathoky, Nepal; Dr Subramaniam Muniandy, Malaysia

Invitees: Dr Russell D'Souza, UNESCO Chair in Bioethics, Australia; Dr S Sharma, Editor-IJCP Group

Key points from the discussion: Six things to remember in COVID-19

If you do not have COVID-19, ask yourself

- **"Am I at risk"?** Age, sex (males more at risk), am I vaccinated (flu, pneumonia, MMR, BCG), do I have any comorbid condition, am I immunocompromised, is my profession high risk, e.g., healthcare worker dealing with microdroplets.
- **"Is my environment at risk"?** My room, my office, travel, kitchen, drawing and dining table, toilet – are they well-ventilated or not.
- **"Am I prepared"?** Who will be my treating doctor, which hospital if I need admission, do I have stand-by oxygen, first aid box, notification (who should I notify), which lab for home test?
- **"What do I do if I get it"?** Do I need to isolate/quarantine/inform contacts, interpretation of rapid antigen test or RT-PCR; start observing for symptoms; start treatment for Day 1.
- **Observation days:** 1-6 days (watch for hypoxia complications), Day 9 (allowed to meet family), Day 14 (no quarantine), Day 28 (consider plasma donation), Day 40, Day 90.

- **0-9 days:** Nutrition, 6-minute walk test (6MWT), cohort isolation, blood tests, tele-consult, treatment.
- **9-90 days:** Observe (for post-COVID symptoms), appeal, plasma donation, antibodies, antigen Ct value, nutrition.

Six things to do to tackle COVID-19

- During first 6 days (6 am, 6 pm) 6MWT, 6 parameters, 6 feet distance (ideal).
- **6 parameters:** Shortness of breath, cough or difficulty talking, SpO_2, increase in temperature, distance and heart rate.
- **6 tests on Day 1:** CBC with ESR, CRP, lactate dehydrogenase (LDH), ferritin, D-dimer, IL-6.
- **Six instruments at home:** SpO_2 monitor, peak expiry flow rate (PEFR), BP, thermometer, glucometer, smell and taste.
- **Six gene targets:** E, N, S, RdRp, ORF 1a, ORF 1b; gene targets may remain in the body for about 120 days.
- **Reception** (whosoever visits my home): Jaggery (taste), rose (smell), wash feet/hands, namaste (greet), ask to sit a higher place (no face-to-face meeting).
- **Decontaminate**: 6 g bleaching powder in 900 mL water to make 0.1% solution.
- **6 Treatment options:** Oxygen, plasma, steroids, heparin, antibiotics and antiviral.

Six things for prevention

- Contact time in last 48 hours, contact distance (was it <6 feet [ideal]), was the area cross ventilated, was the person wearing a mask and was the person coughing/sneezing.
- **Appeals (ask for):** Prevent, test, home (quarantine), cohort (two COVID-positive persons can stay in isolation together), Day 9, Day 14 (stop quarantine, shift to monitoring).
- **6 ways to clean and sanitize:** Soap, sanitizer, disinfectant, UV, ozone and air purifier.
- **6 tastes:** Astringent, bitter, pungent, sweet, sour and salt. In COVID-19, salt and bitter tastes are retained, while the rest are lost.
- **Mistakes:** Missing first case in your family, first cluster in your colony, first spread, misinterpreting antigen/antibody test, missing Days 1-3 (pneumonia develops on Day 3).
- **6 supplements:** Vitamin C, D, B12, iron, zinc and thymosin alpha.

Six things about the virus

- **Six different behaviors:** Viral, bacterial, HIV-like, it causes immune-inflammation (antigen triggered), thrombo-inflammation and cytokine storm.
- **Six strains:** L strain (original strain in Wuhan), strains S, V, G, GR and GH.
- **New definition:** Acute manageable thrombo-immunoinflammatory disease with post-viral state.
- The CDC has recommended maintaining a distance of 2 m (6 feet), while WHO has recommended maintaining a distance of 1 m (3 feet) as 2 m distancing may be difficult in developing countries.
- The third wave in Hong Kong is coming down from 114 new cases in a day in July to 18 cases/day now. Hong Kong will launch en masse population screening program to identify silent carriers; screening will be voluntary. Should the rules about social gatherings be relaxed is a dilemma because of apprehension of another wave of the infection, which might exhaust the resources.
- The first sero-survey (done between June 27 and July 10) in Delhi showed 22.8% seroprevalence; the second sero-survey (done in the first week of August) shows a seroprevalence of 28.3% (males 28.3%, females 32.2%, <18 years 35%, 18-49 years 29%, >50 years 31%).
- Seroprevalence is 51.5% in Pune; in Mumbai, it is 57% in slums and 16% in residential societies. A study in Bangladesh conducted by the Institute of Epidemiology, Disease Control and Research and the International Centre for Diarrhoeal Disease Research, Bangladesh in Dhaka (RT-PCR) has shown 9% of population in Dhaka has the infection.
- Nepal is testing for COVID-19 with GeneXpert test for emergency cases; it has 100% specificity, but sensitivity is around 50%. RT-PCR is the gold standard.
- Singapore is reaching the tail end of the outbreak in dormitories; community cases in the last week have been 0-2 in a day. Challenge is the next wave of infection, opening up of economy. Singapore is looking to open up travel to selected destinations.
- Malaysia has detected D614G strain of the virus (mutation of SARS-CoV-2 virus) in a cluster of cases, which has been termed as the "Sivaganga cluster". The index case belongs to Sivaganga in Tamil Nadu.
- In Australia, all travel within the country has been stopped. Cases are coming under control in Victoria.

With input from Dr Monica Vasudev

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News and Views

FDA OKs Targeted Treatment for Rare Duchenne Muscular Dystrophy Mutation

The US Food and Drug Administration (FDA) has given accelerated approval to viltolarsen injection to treat Duchenne muscular dystrophy (DMD) in patients with a confirmed mutation of the DMD gene, amenable to exon 53 skipping.

Viltolarsen becomes the second FDA-approved targeted treatment for patients with such a mutation. Nearly 8% of patients with DMD are reported to carry a mutation that is amenable to exon 53 skipping. The drug was assessed in two clinical studies with 32 patients with genetically confirmed DMD. Increase in dystrophin production was shown in one of the two studies, including 16 DMD patients, with 8 patients given viltolarsen at the recommended dose. Dystrophin levels were shown to increase, on average, from 0.6% of normal at baseline to 5.9% of normal at Week 25… (*FDA*)

Lupus Anticoagulant Linked with COVID Thrombosis

Prothrombotic autoantibodies were shown to be raised in coronavirus disease 2019 (COVID-19) and associated with the development of thrombosis, suggested a small observational study.

Lupus anticoagulant (LA) was found in 44% of COVID-19 patients tested compared to 22% of other patients (30 of 68 vs. 27 of 119, p = 0.002), reported researchers in *JAMA Network Open*. In the COVID-19 group, 63% of the LA-positive patients had documented arterial or venous thrombosis compared with 34% of the LA-negative patients (p = 0.03). C-reactive protein (CRP) was higher with LA positivity but had no link with thrombosis. LA continued to be a significant independent predictor of thrombosis after adjusting for CRP, with an odds ratio (OR) of 4.39… (*Medpage Today*)

Supplement-Probiotic Combo may Improve Depressive Symptoms

According to new research, a combination of the supplement S-adenosylmethionine (SAMe) and the probiotic bacteria *Lactobacillus plantarum* (*L. plantarum*) HEAL9 may speedily relieve the symptoms of depression and anxiety.

Investigators from Italy randomized 90 patients with subthreshold or mild-to-moderate depression to receive either SAMe + *L. plantarum* HEAL9 or placebo for a duration of 6 weeks. Significant reductions were noted in depression, anxiety and cognitive symptoms as early as 2 weeks following treatment initiation. On comparing the effects of the combination of SAMe and *L. plantarum* HEAL9 with placebo, it was noted that in the treatment group, there were greater reductions in Zung self-rating depression scale (Z-SDS) total score at 2 weeks (–2.78; 95% confidence interval [CI], –5.33 to –0.23, p = 0.0330) and at 6 weeks (–3.55; 95% CI, –6.43 to –0.67; p = 0.0165). The study was published online in *Primary Care Companion CNS Disorders*… (*Medscape*)

NIAID Testing Remdesivir *plus* MS Drug for COVID-19

A randomized controlled trial is currently ongoing to test the safety and efficacy of the broad-spectrum antiviral remdesivir in combination with the immunomodulator interferon beta-1a, a drug used to treat multiple sclerosis, for patients with COVID-19.

The Adaptive COVID-19 Treatment Trial 3 (ACTT-3), sponsored by the National Institute of Allergy and Infectious Diseases (NIAID), will enroll over 1,000 adults hospitalized with COVID-19 at up to 100 centers in the United States and abroad.

ACTT-1 noted that among patients hospitalized with COVID-19 who were administered a 10-day course of remdesivir, time to recovery was significantly shorter in comparison with those who received placebo. Preliminary results of ACTT-3 are expected by fall this year… (*Medscape*)

Recent-onset Diabetes, Weight Loss Linked with Cancer in 30-year Study

Individuals with recent-onset diabetes associated with weight loss appeared to have an increased risk for pancreatic cancer and could benefit from surveillance, suggest researchers.

A study published online in *JAMA Oncology* revealed that in a cohort of 1,59,025 individuals followed for a duration of 30 years, those with recent-onset diabetes and weight loss of 1-8 lbs were found to have over threefold risk for pancreatic cancer (hazard ratio [HR] 3.61, 95% CI 2.14-6.10) compared to those without

diabetes or weight loss. Those with recent-onset diabetes and weight loss more than 8 lbs had nearly seven times the risk (HR 6.75, 95% CI 4.55-10.0)… (*Medpage Today*)

NAFLD a Predictor of Arrhythmia Recurrence Post-AF Ablation

New research suggests that nonalcoholic fatty liver disease (NAFLD) confers a higher risk for arrhythmia recurrence after atrial fibrillation (AF) ablation.

Over 29 months of follow-up post-ablation, 56% of patients with NAFLD had bouts of arrhythmia, compared with 31% of those without NAFLD, matched for age, sex, body mass index (BMI), ejection fraction within 5% and AF type ($p < 0.0001$). Presence of NAFLD independently predicted arrhythmia recurrence in multivariable analyses adjusted for multiple confounders, including A1c, BMI and AF type (HR, 3.0; 95% CI 1.94-4.68). Of note, no NAFLD patient in the study who lost at least 10% of their body weight had recurrent arrhythmia, compared to 31% who lost <10%, and 91% who gained weight prior to ablation ($p < .0001$)… (*Medscape*)

Mammography Beginning at 40 Reduces Risk of Breast Cancer Death

Yearly mammography from 40 to 49 years of age was associated with a significant 25% reduction in breast cancer mortality during the first 10 years of follow-up, suggest data from the UK Age Trial.

Investigators calculated that 1,150 women needed to undergo screening in the age group of 40-49 years to prevent one breast cancer death, or about one breast cancer death prevented per 1,000 screened. Several guidelines recommend starting screening for breast cancer at age 50. However, researchers in the present study state that screening prior to age 50 could prevent deaths from breast cancer, with a minimal additional burden of overdiagnosis. The findings are published online August 12 in *Lancet Oncology*… (*Medscape*)

FDA Approves Treatment for NMOSD

The US FDA has granted approval to satralizumab-mwge for the treatment of neuromyelitis optica spectrum disorder (NMOSD) in adults with a particular antibody. This includes patients who are anti-aquaporin-4 or AQP4 antibody-positive.

NMOSD, a rare autoimmune disease of the central nervous system, primarily affects the optic nerves and spinal cord. This drug is the third approved treatment for the disorder. The effectiveness and safety of the drug were shown in two 96-week clinical studies. In the first study, treatment with satralizumab-mwge led to a reduction in the number of NMOSD relapses by 74% in anti-AQP4 positive patients compared to treatment with placebo. In the second study, the drug reduced the number of relapses in anti-AQP4 positive patients by 78% compared to placebo… (*FDA*)

Heartburn Drug may Help COVID-19 Patients

More data from observational studies has shown that famotidine, used for the treatment of heartburn, was associated with improved clinical outcomes in COVID-19 patients.

Use of famotidine in 83 patients was linked with a lower risk of in-hospital mortality and a combined outcome of death and intubation, reported researchers. Famotidine was also found to be associated with lower levels of serum markers for severe disease, noted the authors in the *American Journal of Gastroenterology*. In a sample of 878 patients, about 10% were administered famotidine. Use of famotidine was tied to reduced risk of hospital mortality (OR 0.366, 95% CI 0.155-0.862, $p = 0.021$), and a decreased risk of the combined death or intubation endpoint (OR 0.495, 95% CI 0.228-0.965, $p = 0.04$). Intubation occurred in 22% patients in the famotidine group compared to 32% in the nonfamotidine group… (*Medpage Today*)

COVID-19 Effects on Thyroid Gland

Rates of thyrotoxicosis appear to be significantly higher among patients who are critically ill with COVID-19 compared to critically ill patients who do not have COVID-19, suggests new research.

The study, published online in *The Lancet Diabetes and Endocrinology*, compared critically ill intensive care unit (ICU) patients with COVID-19 with those who did not have COVID-19 or who had milder cases of COVID-19. The study revealed that thyroid disorders do not increase the risk of developing COVID-19. Researchers, however, stated that routine assessment of thyroid function should be done in patients with COVID-19 who need high-intensity care as they often present with thyrotoxicosis due to a form of subacute thyroiditis related to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)… (*Medscape*)

Bariatric Surgery and Fewer BP Medications

Obese patients with hypertension who underwent bariatric surgery experienced a reduction in the medications needed to achieve blood pressure (BP) control, suggests the GATEWAY trial.

In the 100-person study, 73% of those who underwent Roux-en-Y gastric bypass (RYGB) compared to 11% of controls on medical therapy alone could achieve at least a 30% reduction in total number of antihypertensive medications while maintaining BP <140/90 mmHg at 3 years, reported researchers in *Annals of Internal Medicine*. Certain secondary endpoints were also in favor of the bariatric surgery group: Use of antihypertensives: median one vs. three medications; BP control to <140/90 mmHg without medications: 35% vs. 2%; BP control to <130/80 mmHg without medications: 31% vs. 0%... (*Medpage Today*)

Systolic Orthostatic Hypotension Linked with Dementia Risk

Systolic, but not diastolic, orthostatic hypotension has been found to be associated with a 40% rise in the risk for incident dementia in a new study published online in *Neurology*.

The risk is not affected by demographic variables or medical comorbidities, suggests the new research. Data from the prospective Health, Aging and Body Composition (Health ABC) study revealed that variability over time in postural changes in systolic BP was linked with an increased risk for dementia. According to investigators, this could be the first time that such an association has been observed. Variability in postural changes in diastolic BP was shown not to have a link with increased dementia risk… (*Medscape)*

Povidone-iodine to Prevent SARS-CoV-2 Infection

SARS-CoV-2, a novel coronavirus, known to cause COVID-19, surfaced in Wuhan, China towards the end of the year 2019. The World Health Organization (WHO) declared the COVID-19 outbreak as a public health emergency of international concern on January 30, 2020.

While there is lack of an effective treatment strategy for COVID-19, preventive measures are being recommended by various leading organizations, including the WHO. A paper published in *Lancet Infectious Diseases* noted that high viral loads in samples obtained from the upper respiratory tract pointed to a high risk of transmission during the early days following the onset of symptoms.[1] It appears that asymptomatic patients can also transmit the infection.[2] Diminishing the viral load thus seems to be a potential strategy to check the transmission of this viral illness.

Povidone-iodine (PVP-I) has long been in use as a broad-spectrum microbicidal agent which can cause inactivation of bacteria, fungi, protozoans and viruses. It has potential virucidal activity and has even been shown to have the highest virucidal activity among several antiseptics, including chlorhexidine gluconate (CHG), benzalkonium chloride (BAC), benzethonium chloride (BEC) and alkyldiaminoethyl-glycine hydrochloride.[2] PVP-I gargle, has been shown *in vitro*, to inactivate adenovirus, mumps, rotavirus, poliovirus (types 1 and 3), coxsackie virus, rhinovirus, herpes simplex virus, rubella, measles, influenza and human immunodeficiency virus (HIV). This antiseptic formulation is therefore a broad-spectrum virucidal agent that inactivates both enveloped and nonenveloped viruses. The agent is also effective against Middle East respiratory syndrome coronavirus (MERS-CoV) and SARS-CoV.[2]

PVP-I has been shown to have virucidal activity against SARS-CoV-2 as well. PVP-I products, including gargle and mouth wash, were shown by Anderson et al,[3] to attain ≥99.99% virucidal activity against the virus. The agent was reported to have a rapid virucidal activity against this virus.

Working out ways to minimize the viral titers in saliva and nasal mucosa from COVID-19 patients could possibly curb the transmission of the disease.[4] PVP-I could be used to prevent the spread of virus-containing droplets from the nose and mouth of an infected person.

PVP-I could reduce the viral load in the nasal and oral mucosa of COVID-19 patients and limit the risk of transmission.[4]

Use of PVP-I products for oral decontamination, along with following distancing measures, frequent handwashing and use of masks could go a long way in preventing the transmission of the SARS-CoV-2 virus.

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Pollution Tied to First Time Asthma in Children: Study

The more children are exposed to pollution, the greater the risk they have of developing their first case of asthma, suggested a large study published in the *BMJ*.

The study has added to the increasing evidence base that exposure to air pollution affects the development of chronic breathing problems. Investigators assessed data from around 7,80,000 Danish children born between 1997 and 2014, and followed up with the records to determine if any of the children developed persistent wheezing and asthma between 1 and 15 years of age. Children whose parents had asthma had a higher likelihood of having asthma, as did children whose mothers smoked during pregnancy.

After adjusting for these factors, when the children were exposed to higher levels of small particle pollution and nitrate pollution, they were found to be more likely to develop asthma and persistent wheezing compared to children who were not exposed… (*CNN*)

Robotic Surgery Improves OS in Early Oropharyngeal Cancer

A retrospective study, published in *JAMA Oncology*, has revealed that transoral robotic surgery (TORS) could improve surgical outcomes and survival in comparison with nonrobotic surgery in patients with early-stage oropharyngeal cancer.

The study included 9,745 patients from the National Cancer Database (NCDB). About 27.6% of these patients underwent TORS. The robotic procedure was linked with lower rates of positive surgical margins, decreased odds of receiving adjuvant chemoradiotherapy and improved overall survival (OS). Additionally, among the 4,071 patients with known human papillomavirus (HPV) status, robotic surgery was found to be associated with improved OS… (*Medpage Today*)

Influenza Vaccination Critical During Pandemic: CDC

The Centers for Disease Control and Prevention (CDC) has urged all people who do not have any contraindications to receive the influenza vaccine for the 2020-2021 influenza season. The agency says that it is even more critical to receive the vaccination during the COVID-19 pandemic compared to the normal years.

Authors of recommendations, published August 20, in *Morbidity and Mortality Weekly Report*, state that influenza vaccination of persons aged 6 months and above to reduce the prevalence of influenza illness will have a role in decreasing the symptoms that might be confused with those of COVID-19.

The CDC Advisory Committee on Immunization Practices (ACIP) recommends routine yearly influenza vaccination for all those aged 6 months and older who do not have any contraindications to the vaccine… (*Medscape*)

Older Age and Male Sex Increase Cancer Risk in Lupus

According to a large multicenter cohort study, among patients with systemic lupus erythematosus (SLE), cancer risks are associated with older age at diagnosis and male sex, while lung cancer specifically is associated with smoking.

A multivariable analysis revealed that the HR for any type of cancer among patients included in the Systemic Lupus International Collaborating Clinics Inception Cohort was 1.05 (95% CI 1.03-1.06) for greater age at baseline. The risk for women was lower, with a HR of 0.47 (95% CI 0.26-0.85). History of smoking >15 cigarettes/day was tied to an almost sevenfold increased risk for lung cancer (HR 6.64, 95% CI 1.43-30.9). The findings were published in *Arthritis Care & Research*… (*Medpage Today*)

WHO Cautious on COVID-19 Plasma, US Issues Emergency Use Authorization

The WHO is wary about supporting the use of recovered COVID-19 patients' plasma to treat those who are ill.

The agency has stated that the evidence that convalescent plasma works is of low quality. The US FDA has authorized the use of convalescent plasma. WHO chief scientist, Soumya Swaminathan, said that that there are only a few clinical trials of convalescent plasma that have produced results, and the evidence available is not convincing enough to support the use of plasma therapy beyond an experimental treatment. She added that though some trials have showed some benefit, they are small and the data has been inconclusive thus far… (*ET Healthworld – Reuters*)

First Brain Stimulation Device Cleared to Help Smokers Quit

The US FDA has granted marketing approval for the BrainsWay deep transcranial magnetic stimulation (TMS) system to assist adult smokers quit tobacco.

The system has already received FDA approval as a treatment for patients with obsessive-compulsive disorder and major depressive disorder.

This deep TMS system has H4-coil and targets addiction-related brain circuits. A prospective, double-blind, randomized, sham-controlled, multicenter study included 262 adults with a history of smoking an average of over 26 years and had multiple failed attempts to quit. In the full intention-to-treat population (262 subjects), the 4-week continuous quit rate (CQR, the primary endpoint) was 17.1% in the active deep TMS group compared to 7.9% in the sham TMS group (p = 0.0238)… (*Medscape*)

Coffee Intake During Pregnancy Tied to Negative Birth Outcomes

Even at moderate levels, coffee intake during pregnancy is associated with negative birth outcomes, suggests a research based on a literature review.

According to the report published in *BMJ Evidence-Based Medicine*, coffee consumption during pregnancy was found to be linked with a heightened risk of adverse pregnancy outcomes including miscarriage, stillbirth and low birthweight or small for gestational age infants. At caffeine doses of 200 mg/day, the estimated risk increase ranged from 14% to 38% for these outcomes relative to no caffeine consumption. Maternal coffee intake was also found to be associated with negative outcomes later in childhood, such as acute leukemia and obesity… (*Medpage Today*)

BP Drugs that may Protect Against Depression

A Danish population-based study has outlined a short list of antihypertensive medications that may be associated with decreased risk of depression.

Significantly lower risk of depression incidence was noted in population-based registries for the ACE inhibitors enalapril and ramipril; calcium channel blockers amlodipine, verapamil and verapamil combinations and the β-blockers propranolol, atenolol, bisoprolol and carvedilol. Diuretics were found to have no link with depression risk.

Investigators also noted that individuals without any antihypertensive prescriptions (possibly those without high BP) had the lowest depression risk, thus indicating that patients with hypertension and cardiovascular and cerebrovascular diseases have an increased risk of developing depression. The findings are published in the September 2020 issue of *Hypertension*… (*Medpage Today*)

Coronavirus Re-infections Raise Concerns

It has been confirmed that two European patients have been re-infected with COVID-19. This has raised concerns about immunity to the coronavirus.

The cases, in Belgium and the Netherlands, have been reported after researchers in Hong Kong reported about a man who got infected by a different strain of the virus 4½ months after recovering. This was the first such second infection to be observed. The findings have raised concerns about the efficacy of potential vaccines against the virus. Experts; however, believe that there need to be many more cases of re-infection for these to be justified… (*Reuters*)

CDC Updates Recommendations for Travelers

The US CDC has updated the recommendations for travelers. It has dropped the requirement for self-quarantine for 14 days after returning from countries or areas with a high concentration of COVID-19 cases.

The updated guidance states that travelers should follow state, territorial, tribal and local recommendations after travel. The state and local governments may require travelers to undergo testing and self-quarantine. CDC states that those who return from a trip should take safety precautions such as wearing a mask, washing hands frequently and practicing social distancing. People who were involved in higher-risk activities must stay at home, avoid contact with people who are at risk of infection and consider getting tested for COVID-19. Higher-risk activities include visiting places with a high concentration of cases, attending a large social gathering and taking a cruise… (*Medscape*)

Laparoscopic Surgery Appears Safe in Early Gastric Cancer

A randomized trial, published in *JAMA Oncology*, has revealed that laparoscopic surgery, performed by an experienced surgeon, is a safe alternative to open surgery for patients with stage I gastric cancer.

The trial included 214 patients undergoing total gastrectomy with lymphadenectomy. There appeared to be no significant differences between the two groups in rates of morbidity and mortality, or intraoperative and postoperative complications. The overall rates of morbidity and mortality within 30 days of surgery were 19.1% and 20.2% in the laparoscopic group and the open surgery group, respectively (rate difference –1.1%, 95% CI –11.8% to 9.6%)… (*Medpage Today*)

West African Nation of Togo Eliminates Sleeping Sickness as a Public Health Problem

The West African nation of Togo has been successful in eliminating human African trypanosomiasis or 'sleeping sickness' as a public health problem. The nation has

become the first in the African continent to achieve the milestone.

Sleeping sickness, a tropical disease, is caused by protozoan parasites of the genus Trypanosoma. If left untreated, the disease is almost always fatal. Dr Matshidiso Moeti, WHO Regional Director for Africa, stated that Togo is a pioneer in eliminating sleeping sickness, a disease that has threatened millions of Africans. She congratulated the Government and people of Togo and stated that these efforts will inspire others to work towards the eradication of sleeping sickness… (*UN*)

COVID-19 Antibodies may Last Only for 50 Days

Mumbai: According to a study conducted on affected healthcare staff of JJ Group of Hospitals, COVID-19 antibodies may not last more than a couple of months.

In this study of 801 people, there were 28 participants who tested positive for COVID-19 (on reverse transcription polymerase chain reaction [RT-PCR]) around late April-early May (around 7 weeks prior). None of them showed any antibodies in a sero-survey done in the month of June, reported the pre-print of the study scheduled to be published in the September issue of the *International Journal of Community Medicine and Public Health*. There were 34 participants in the sero-survey who tested PCR positive 3 weeks and 5 weeks prior, respectively. Around 90% of those in the 3-week group had antibodies, while only 38.5% in the 5-week group were found to have antibodies… (*ET Healthworld – TNN*)

FDA Approves First-in-Class Androgen Inhibitor Acne Cream

The USA FDA has granted approval to clascoterone cream 1%, a first-in-class topical treatment for acne, stated the drugmaker Cassiopea.

This androgen receptor inhibitor is indicated for the treatment of acne vulgaris in male and female patients aged 12 years and above. The drug has been shown to reduce sebum production and inflammation in preclinical and clinical studies. This is the first acne treatment with a new mechanism of action approved in approximately 40 years and is expected to be available in the US around early next year. The approval is based on two clinical trials that noted significant improvement in inflammatory as well as noninflammatory lesions after 12 weeks with twice-daily topical application of the drug… (*Medpage Today*)

Statins Tied to Reduced Mortality in COVID-19

According to a meta-analysis of four published studies, treatment with statins could reduce the risk of a severe or fatal course of COVID-19 by 30%.

The report, published online August 11 in *The American Journal of Cardiology*, included around 9,000 COVID-19 patients. Investigators noted a significantly decreased risk for fatal or severe COVID-19 among patients who were using statins compared to those who were not on statins (pooled HR, 0.70; 95% CI, 0.53-0.94). Based on the findings, the investigators suggest that moderate- to high-intensity statin therapy would likely be beneficial in patients with COVID-19… (*Medscape*)

Phthalate Exposure could Increase ADHD Risk in Teens

Greater exposure to some endocrine-disrupting chemicals (EDCs) has been found to be associated with increased risk of attention-deficit/hyperactivity disorder (ADHD) in teens in a new study.

The study including 205 adolescents and teens noted that every twofold increase in antiandrogenic phthalate concentrations measured in urine samples was associated with a 34% rise in the relative risk (RR) for ADHD (adjusted RR [aRR] 1.34, 95% CI 1.00-1.79). Greater exposure to antiandrogenic phthalates, as noted by the sum of 11 phthalate chemicals, was found to be linked with an increase in hyperactivity problems among adolescents (aRR 1.40, 95% CI 1.07-1.84). The findings are published in *JAMA Network Open*… (*Medpage Today*)

Severe or Fatal COVID-19 Very Rare in Children

Children and young people have lesser likelihood, compared to adults, of getting severe cases of COVID-19 infection, and death from the disease among children is very rare, suggests research from UK.

According to the study of COVID-19 patients admitted to 138 hospitals in Britain, less than 1% were children, and of those, less than 1% died, all of whom were already having a serious illness or underlying health disorders. Malcolm Semple, professor of outbreak medicine and child health at Britain's University of Liverpool, stated that COVID-19, in itself, is not harming children on a significant level. The study is published in the *BMJ*… (*Reuters*)

Anorexia may Restrict Young Women's Growth

Anorexia nervosa may impede the growth and impact the future height of teenage girls, suggests a new study.

Investigators reviewed data from 255 adolescent girls hospitalized for anorexia nervosa at an average age of 15 years. Their height was measured at the time of hospital admission, discharge and at adulthood. The main outcome of adult height was found to be significantly shorter than expected, based on mid-parental target height. The patients' heights increased significantly during hospitalization, from 158 cm to 159 cm; however, the change in height-SDS [standard deviation scores] was nonsignificant and height-SDS at discharge was significantly lower in comparison to what is expected in a normal population. The premorbid height SDS in the study population was similar to normal adolescents; however, the height-SDS at hospital admission, discharge and adulthood were found to be significantly lower than expected (–0.36, –0.34 and –0.29, respectively). The findings are published in the *Journal of Clinical Endocrinology & Metabolism*… (*Medscape*)

Fecal Transplant Seems Promising in Reducing Alcohol Craving

According to a study presented at the Digital International Liver Congress 2020, fecal microbiota transplantation can lead to a short-term reduction in alcohol craving in patients with alcohol-induced cirrhosis who are unable to quit drinking.

This phase 1 double-blind study evaluated 20 men from a Virginia veteran's hospital with untreatable alcohol use disorder who were not eligible for liver transplantation. Ten men were randomly assigned to fecal transplantation and 10 to placebo; one man in each group dropped out of the study. At Day 15, 90% men in the transplant group experienced a reduction in alcohol cravings compared to 30% in the placebo group. At 30 days, levels of creatinine, serum interleukin (IL)-6 and lipopolysaccharide-binding protein were lower in the transplant group compared to the placebo group… (*Medscape*)

Pancreatitis – Another Presenting Sign of COVID-19

As per a retrospective study in a New York health system, COVID-19 patients can present with acute pancreatitis, often idiopathic in origin, with Black and Hispanic patients with pancreatitis having higher likelihood than others to have the infection.

Overall, 17% of pancreatitis patients in the study were positive for COVID-19, thus suggesting that pancreatitis should be included in the list of gastrointestinal (GI) manifestations of this viral infection. Among 48,012 hospitalized patients, 11,883 (24.75%) were positive for COVID-19 at admission. Overall, 189 patients fulfilled the criteria for a diagnosis of pancreatitis (point prevalence 0.39%), and 32 of these 189 (17%) were found to be COVID-19 positive. This accounts for a point prevalence of 0.27% of pancreatitis among patients hospitalized with COVID-19. The findings are published online in *Gastroenterology*… (*Medpage Today*)

Kids can Carry Coronavirus in Respiratory Tract for Weeks, Says Study

The coronavirus can stay in the noses and throats of children for weeks altogether even if they don't show any symptoms, suggests a study from South Korea. This might explain the silent spread of the virus.

The study included data on 91 asymptomatic, presymptomatic and symptomatic children diagnosed with COVID-19 from February 18 to March 31. Around 22% of these patients did not have any apparent symptoms and remained asymptomatic throughout the study period. About 20% were presymptomatic, i.e., they did not appear or feel sick at the time but developed symptoms later. Nearly 78% exhibited symptoms. Just 8.5% of the patients with symptoms were diagnosed with COVID-19 at the time their symptoms started. About 66.2% of the patients with symptoms had symptoms that were not recognized before they were diagnosed, and 25.4% developed symptoms after diagnosis.

Therefore, it appears that children with COVID-19 infection might go unnoticed either with or without symptoms, which could facilitate viral circulation within the community… (*CNN*)

Long, Frequent Naps can Predict Alzheimer's Dementia

Longer, more frequent naps during daytime in elderly adults appear to predict a higher risk of incident Alzheimer's dementia over time, suggested an actigraphy study.

Elderly people who napped more than once a day had 1.3-times higher risk of developing future Alzheimer's dementia, reported a study presented at the virtual SLEEP 2020, a joint meeting of the American Academy of Sleep Medicine and the Sleep Research Society. The study included 1,180 individuals from the Rush Memory and Aging Project. None of the participants had dementia at baseline, while 264 had mild cognitive impairment. The study participants napped for 38.3 minutes and 1.56 times a day at baseline. Overall, 277 participants developed Alzheimer's dementia within a period of 5.74 years. Every 30-minute increase

in the duration of daily napping was found to be linked with a 20% rise in the risk of incident Alzheimer's dementia, after adjusting for age, sex and education… (*Medpage Today*)

90% of Countries Suffer Disruptions to Essential Health Services due to Ongoing Pandemic

The first indicative survey on the impact of COVID-19 on health systems has been recently published by the WHO, which has data from 105 countries.

The data compiled from 5 regions from March through June 2020 suggest that nearly every country, i.e., 90% of them, experienced disruption to the health services, with the greatest impact seen in low- and middle-income countries. Most countries have reported that several routine and elective services have been suspended. Critical care, such as cancer screening and treatment and HIV treatment, has undergone high-risk interruptions in low-income countries.

WHO Director-General, Dr Tedros Adhanom Ghebreyesus, said that COVID-19 should serve as a lesson to all countries and that everyone should better prepare for emergencies and keep investing in health systems… (*WHO*).

COVID-19: Possible Risks to Pregnant Women

Pregnant and recently pregnant women diagnosed with COVID-19 in the hospital seem to have a lesser likelihood of having symptoms of fever and muscle pain but higher odds of being admitted to the intensive care unit, suggests new research published in the *BMJ*.

The study also noted that pregnant women with COVID-19 have a greater risk of delivering preterm, but preterm birth rates were not high. Investigators reviewed 77 studies on COVID-19 in pregnant and recently pregnant women that were published between December 1 and June 26. The studies included data on 13,118 pregnant and recently pregnant women with COVID-19, and 83,486 nonpregnant women of reproductive age with COVID-19. Investigators stated that the symptoms of fever and myalgia are seen less often in pregnant and recently pregnant women compared to nonpregnant women of reproductive age… (*CNN*)

Estrogen may Reduce Severity of COVID-19 Symptoms in Women, Says Study

A review, published in the September online issue of the journal *Current Hypertension Reports*, tried to explore why men have a greater risk for more severe symptoms and worse outcomes from COVID-19 irrespective of age. Investigators carried out a review of the published preclinical data on sex-specific hormone activity, particularly estrogen.

Lead author, Leanne Groban, MD, Professor of Anesthesiology at Wake Forest School of Medicine, part of Wake Forest Baptist Health, stated that coronavirus affects the heart and estrogen protects against cardiovascular disease in women. Therefore, hormonal differences between the sexes seem to be the most likely explanation. According to the researchers, the review also hinted at estrogen lowering the level of ACE2 in the heart. This could possibly alter the severity of COVID-19 in women… (*HT – ANI*)

COVID-19 Patients with Obesity have Higher Viral Load and for Longer

Obese patients with COVID-19 (body mass index [BMI] >30 kg/m^2) appear to have a higher viral load and the virus seems to persist for a longer duration in these individuals, suggests new research.

Preliminary results of the work were presented at the virtual European and International Congress on Obesity (ECOICO) 2020. It was reported that subjects with a BMI >30 kg/m^2 had COVID-19 statuses that became negative 5 days later when compared to those with a BMI <25 kg/m^2. The investigation revealed that individuals with a BMI <25 kg/m^2 and COVID-19 took about 14 days to recover completely, those with BMI 25-30 kg/m^2 took about 17 days, while those in the >30 kg/m^2 BMI category took nearly 19-20 days… (*Medscape*)

Can Air on the Bus Spread COVID-19?

In what seems to be additional evidence for SARS-CoV-2 airborne transmission, passengers who were on a bus with someone having COVID-19 had a greater risk of contracting the virus compared to passengers who rode on a different bus to the same event, suggests a study from China.

In January, 24 of 68 individuals on a bus with one case of COVID-19 in Ningbo city, including the index case, were diagnosed as having COVID-19 afterwards. None of 60 individuals on the second bus, which had no apparent index case, had the infection in the subsequent weeks. People seated closest to the individual had a 60% higher risk of infection compared to those in "low risk" areas; however, this was not statistically significant (RR 1.6, 95% CI 0.8-3.2). The findings are published in *JAMA Internal Medicine*… (*Medpage Today*)

Indian Journal of Clinical Practice, Vol. 31, No. 4, September 2020

The Spiritual Prescription "I am Sorry"

KK AGGARWAL

Two hardest words for a doctor to say: "I'm sorry."

Most defense lawyers counsel doctors to not apologize to patients. Their view is that if you say you're sorry for something, you are implicitly taking some degree of responsibility for whatever has happened. In other words, you are pleading guilty. The complainant's lawyers may use a doctor's apology to the maximum extent possible to show the doctor knew what they did was wrong. The usual approach is deny and defend. But,

- Apologizing after a medical error is the humane thing to do.
- Patients often sue simply because it's the only way to find out what went wrong.
- Erecting a wall of silence is "enough to make someone very angry". And it's awfully easy for an angry person to find a lawyer who will listen to them. At that point, it's too late to say sorry.
- Over 35 states in the USA have passed laws prohibiting doctors' apologies from being used against them in court (apology laws).
- By promptly disclosing medical errors and offering earnest apologies and fair compensation, one can hope to restore integrity to dealings with patients, make it easier to learn from mistakes and dilute anger that often fuels lawsuits.

Apology, the spiritual answer

- The word 'sorry' is synonymous with apology.
- To err is human, but to be able to admit one's error is superhuman.
- Sorry should be heart-felt and not ego-felt. You should not only say sorry but also appear as being genuinely sorry.
- Tremendous courage is required when you face the victim of your wrong doing and apologize to him.
- People who are in harmony with their life and with themselves, find it easy to say "I'm sorry". These people are at peace only after making amends for their wrong doings.
- The word 'sorry' is infused with so much power. Within a fraction of a second, grave mistakes are diluted and estranged relations are brought to life, animosity and anger are dissolved, misunderstandings are resolved resulting in harmony.
- To forgive and forget is a common spiritual saying.
- Remember, we all make mistakes and seek forgiveness from GOD every day.

Group Editor-in-Chief, IJCP Group

■■■■

FDA Approves First-of-its-kind Automated Insulin Delivery and Monitoring System for Pediatric Patients

The US FDA has granted approval to a hybrid closed loop diabetes management device aimed at automatically monitoring glucose and providing appropriate basal insulin doses, for individuals with type 1 diabetes aged 2-6 years. The device would require little or no input from the users or their caregivers.

This 770G System is a first-of-a-kind device intended for use by patients aged 2-6 years. It is also the first legally marketed device that has the ability to automatically adjust insulin delivery depending on the continuous glucose monitor values for this patient population. This is a bluetooth-enabled version of the previously approved 670G System, besides other modifications. This hybrid closed loop system measures glucose levels in the body every 5 minutes and adjusts insulin delivery by either administering or withholding insulin… (*FDA*)

Laughter is the Best Medicine

Several years ago, Norman Cousins was diagnosed as terminally ill and was given 6 months to live. He was told that his chance for recovery was 1 in 500.

He came to realize that worry, depression and anger in his life had contributed to his disease. He started wondering that if illness could be caused by negativity, could wellness be created by positivity.

He thought of making an experiment of himself. Laughter was among the most positive activities he could think of. He rented several funny movies including those of Keaton, Chaplin, Fields and the Marx Brothers. He read funny stories, asked his friends to call him whenever they said, heard or did something funny.

He could not sleep many a times due to his pain, but he noted that laughing for 10 minutes relieved his pain for several hours, so that he could sleep. Eventually, he completely recovered from his illness and lived another 20 happy and healthy years. He talked about his journey in his book "Anatomy of an Illness". He credits his recovery to visualization, the love of his family and friends, and laughter.

People sometimes think that laughter is a waste of time. It is a luxury, they may say. But that's not the truth. Laughter is essential for our equilibrium and our well-being. Laughter helps us get well and stay that way.

Since Cousins' subjective work, scientific studies revealed that laughter has a curative effect on the body, the mind and the emotions. Indulge in laughter as often as you can.

Use whatever makes you laugh – movies, sitcoms, books, cartoons, jokes and friends. Laugh long and loud. People may think you're strange, but sooner or later they'll join in even if they don't know what you're laughing about.

Some diseases may be contagious, but none of them is as contagious as the cure - laughter.

■■■■

Opening Up without Control of COVID-19 would be Disastrous, Says WHO

Countries that are facing significant active spread of COVID-19 must prevent the intensifying events, as opening up without controlling the virus would turn out to be disastrous, stated the WHO.

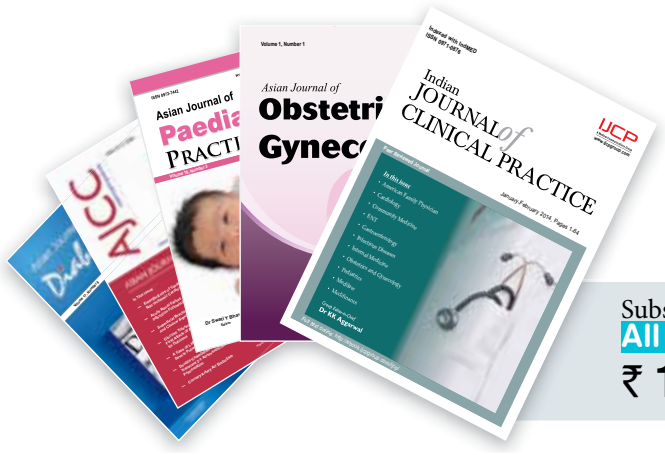
According to WHO Director-General, Dr Tedros Adhanom Ghebreyesus, people are getting tired of restrictions imposed due to the COVID-19 pandemic and want to return to normality. He added that the WHO is in support of efforts to reopen economies and societies, but wants it to be done safely. He further stated that no country can pretend that the pandemic is over and that opening up without control is a 'recipe for disaster'… (*Reuters*)

India Records Around 2 Million COVID-19 Cases in August, Sets Global Record

New Delhi: India reported around 2 million COVID-19 cases in the month of August, the highest number recorded in any country for any month since the outbreak of the pandemic.

India also recorded a rise in deaths from the coronavirus, with 28,859 fatalities reported in August, representing a 50% escalation from the previous month's toll.

There have been 19,87,705 COVID-19 cases during August in the country, according to data obtained from state governments, thus making it the worst outbreak of COVID-19 in any country in a single month. The US had reported 19,04,462 infections in July. The US and Brazil; however, reported a higher death toll than India during the month of August… (*ET Healthworld – TNN*)



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Lighter Side of Medicine

HUMOR

THREE VAMPIRES WALK INTO A BAR

Three vampires walk into a bar and sit down at a table. The waitress comes over and asks the first vampire what he would like. The first vampire responds, "I would like some blood."

The waitress turns to the second vampire and asks what he would like. The vampire responds, "I would like some blood."

The waitress turns to the third vampire and asks what he would like. The vampire responds, "I would like some plasma."

The waitress looks up and says, "Let me see if I have this order correct. You want two bloods and a blood light?"

A BAD HEADACHE

Doctor, Doctor Have you got something for a bad headache?

Doc: Of course. Just take this hammer and smash yourself in the head.

Then you'll have a bad headache.

AT NINETY-NINE

When a grandmother was in her late eighties, she decided to move to Israel. As part of the preparations, she went to see her doctor and get all her charts. The doctor asked her how she was doing, so she gave him a litany of complaints - this hurts, that's stiff, I'm tired and slower, etc.

He responded with, "You have to expect things to start deteriorating. After all, who wants to live to 100?"

The grandmother looked him straight in the eye and replied, "Anyone who's 99."

BLONDE STOP

A police car pulled alongside a speeding car on the motorway. Glancing at the car he was astonished to see that the blonde behind the wheel was knitting!

Realizing that she was oblivious to his flashing lights and siren, the cop rolled down his window and shouted "Pullover!" The blonde rolled down her window and yelled back "No, it's a scarf!"

AND I WORK IN THE DARK!

A doctor of psychology was doing his normal morning rounds, and he entered a patient's room to find his patient sitting on the floor, sawing at a piece of wood with the side of his hand.

Meanwhile, another patient was in the room, hanging from the ceiling by his feet. The doctor asked his patient what he was doing, sitting on the floor.

The patient replied in an irritated fashion, "Can't you see I'm sawing this piece of wood in half?"

The doctor inquired, "And what is the fellow hanging from the ceiling doing?"

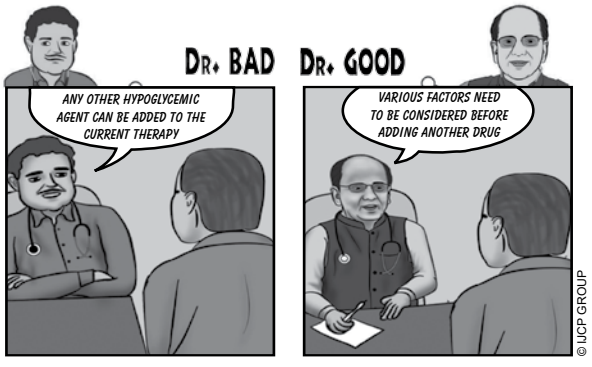
"Oh. He's my friend, but he's a little crazy. He thinks he's a light bulb."

The doctor asks, "If he's your friend, don't you think you should get him down from there before he hurts himself?"

"What? And I work in the dark!?!"

Dr. Good and Dr. Bad

SITUATION: A 62-year-old man with type 2 diabetes who was on monotherapy was advised treatment intensification.



LESSON: Various factors have been identified that drive the choice of treatment at any stage of intensification. These include age, HbA1c, BMI, renal and cardiac morbidity and treatment history.

Clin Ther. 2017;39(11):2296-2310.e14.

IJCP SUTRA: *"Avoid close contact with people who are sick. When you are sick, keep your distance from others to protect them from getting sick too."*

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Should contain the title, short title, names of all the authors (without degrees or diplomas), names and full location of the departments and institutions where the work was performed, name of the corresponding authors, acknowledgment of financial support and abbreviations used.

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Books

Stansfield AG. Lymph Node Biopsy Interpretation Churchill Livingstone, New York 1985.

Articles in Books

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