Annals of the National Academy of Medical Sciences (India)
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This issue of the Annals opens with two important and most relevant articles related to medical education and research in India. Prof. Shridhar Sharma is a veteran medical educationist and administrator. He and his colleague has traced the history and described the current status of medical education in India. This is an excellent treatise on the existing health scenario in the country, including the National health status indicators and highlighting the current health system in the country. Author has delved into the history of medical education in India starting from the philosophy of Ayurveda prevalent from 800 BC onwards, Siddha and Unani medicine have also been touched. The main review, however focuses on growth of medical education in Independent India with respect to allopathic system. ROME (reorientation of medical education), now into history, was a significant venture taken in collaboration with World Health Organization (WHO) in 1977. Each medical college was supposed to establish a well-knit rural referral system. However, lack of necessary infrastructure, logistics, and poor motivation of faculty led to only a partial success. The main emphasis on community-oriented training was also not fulfilled. National Health Policy (1983) was the next step to streamline medical education in India. Efforts following the release of this policy are discussed in detail. The article then goes on to discuss the Medical Council of India, its regulations for selection of medical students, teachers and their promotions, existing curriculum and objectives of graduate medical education. Dr. Sharma has very aptly analyzed the strengths and weakness of the present system of medical education in India. Inadequacy of faculty development is also highlighted. The paper ends with the issues and predictions for future. Professor Sharma concluded with the need for a better equipped physician in the 21st century.

The second article by Ghosh and Ghosh touches on the other side of the coin: research in medical colleges. Authors believe that several factors are responsible for poor quality of research in these institutions, based on evidence generated from various studies and papers published in indexed journals between 1985 to 2017. These factors were identified as poor infrastructure, high patient load, lack of faculty members with adequate research exposure, private practice, lack of incentive, motivation and funds for research. Authors feel that the quality of teachers in medical colleges needs much to be desired. They are particularly not tuned and trained for carrying and supervising research. The last part of the article focuses on the solutions suggested by the authors; and how can the faculty in medical colleges be engaged in research. A heavy emphasis has been laid on to augmenting and changing the way community medicine is being taught.

In a nutshell, both these papers by Dr. Sharma and by Ghosh and Ghosh very aptly describe the current scenario and bottlenecks in medical education and research in Indian medical schools. Authors of both papers have called for a major reforms in the medical curriculum, so as to benefit the physician and the community he/she is going to serve as a benefactor.
Besides these two main articles, there are papers from other specialties including neurology, otorhinolaryngology, and orthopedics.

In the first specialty article for this issue, UK Misra from SGPGIMS, Lucknow reviews the clinical and experimental studies in Japanese Encephalitis. The author summarizes the important clinical, radiological, neurophysiologic and biochemical studies. A syndromic approach is advised to categorize the patient of acute encephalitic syndrome (AES) into neurologic and systemic group. Acyclovir therapy is recommended for the neurologic group. In systematic group, treatment with doxycycline for scrub typhus, artesunate for malaria, ceftriaxone for leptospirosis, and fluid management for dengue are recommended.

Saurabh Varshney discusses their experience of treating 72 cases of pituitary tumor by endoscopic trans-nasal trans-sphenoidal approach between 2015-2016 in adults. Complications rate was less than 10%. Author concluded that endoscopic trans-sphenoidal approach is less traumatic and permits good visualization with overall reduced hospital stay and lesser complications.

The next article by Nair et al from the Department of Orthopedics, AIIMS, Delhi bring about the first of its kind systemic study describing the clinical aspects, prevalence, and imaging features of adhesive capsulitis of the shoulder (ACS) in 16 patients with type-1 diabetes. Presence of retinopathy and limited joint mobility were recognized as independent predictors for ACS in these patients. Imaging confirms the diagnosis and facilitates institution of early therapy.

Sharma et al from AIIMS, Jodhpur report a case of 23-year-old primigravida at 32 weeks gestation with complex congenital heart disease. Her course during the pregnancy is described. Despite a turbulent hospital stay, she delivered a live boy without any complications. The newborn was healthy and did not have a heart defect. Favorable outcome could be achieved by a meticulous planning and multidisciplinary team management.

To end this issue, we present a mini-review by Jyotsna Kailashiya from the biochemistry department of Institute of Medical Sciences, Banaras Hindu University on platelet-derived microparticles (PMPs). These particles have been proposed as potential biomarkers for several conditions such as myocardial infarction, stroke, venous thrombo-embolism, etc. Biosensors are new analytic tools that are now being designed for analysis of PMPs. Author compiles these designs and discusses their pros and cons.

Hope you will enjoy reading this issue.

Dr. Kuldeep Singh
**Medical Education in India**

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**ABSTRACT**

India, a country with rich cultural and health care heritage has progressed by leaps and bounds since independence. The health indices have improved and mortality and morbidity have come down significantly. The health care system of India is a mix of public and private sector. In 2017, there are 479 medical colleges in India with admission capacity of over 60,000 at the undergraduate level. The pattern of modern medical education is modeled after the British system and the first few medical schools were established in 19th century. Medical Council of India (MCI), the government-mandated regulatory agency for medical education, was formed in 1934. The Government of India is regularly reviewing the existing medical education policy to give it a new direction so as to make the curriculum relevant and responsive to the national needs. The MCI has also recognized the need to reduce the artificial compartmentalization of the curriculum into preclinical, para-clinical and clinical disciplines. Horizontal and vertical integration is being promoted but not practiced in most medical colleges. Instruction remains teacher-based and not much emphasis has been laid on self-directed learning. There is a paucity of innovative approaches and lack of adapting the recent technology into most medical schools in India. Skills such as related to communication and managerial domains, and professionalism are not imparted in the current curriculum. While the level of knowledge in the medical sciences is highly unsatisfactory, medical graduates are often found to be lacking in the clinical skills. So far, attempts to introduce innovations in medical education have been limited to certain institutions. Also, there is lack of adequate motivation and opportunities for faculty development. It is strongly felt that there is a need to redefine the goals of medical education in India depending upon the needs of the society. MCI has recently attempted designing a need-based curriculum. At present, medical education in India is at a significant juncture with initiatives coming from both external and internal influences, and the political will to attain the goal of health for all, India hopes to be in a better position to prepare physicians for the 21st century.

**Keywords:** History of medical education in India, health care system in India, traditional system of medicine, medical teaching curriculum, development of medical teachers, National Health Policy.

**General**

India is one of the oldest civilizations and has a rich cultural and health care heritage. It has achieved much socioeconomic progress during the 70 years of its independence. India has become self-sufficient in agricultural production and is now emerging as a fast developing country in the world. The country covers an area of 3,287,240 sq km and extends from the snow covered Himalayan heights to the tropical rain forests of the south. The mainland comprises four regions, namely the great mountain zone, the plains of the Ganga and the Indus, the desert region and the southern peninsula.
Situated entirely in the northern and eastern hemisphere, the mainland lies between latitudes 8.6 degrees and 37.6 degrees north, and between longitudes 68.7 degrees and 97.25 degrees east. The country is about 3050 km in length and 2950 km in breadth. The land frontiers total about 15,200 km while the total length of the coastline of the mainland, Lakshadweep Islands and Andaman and Nicobar Islands is 7516 km.

India’s current population is 1,349,740,568 (1.34 billion) as of October 14, 2017. India has 638,000 villages and 72.2 percent of the total population lives in the rural areas (1). The national average for sex ratio in 2017 is 945 females per 1,000 males. The second most populous country in the world, India is the home of almost 17.90 percent of the world’s population; and the country accounts for 2.42 percent of the world’s total area.

India’s constitution envisages the establishment of a new social order, and one of the primary duties of the individual states is to improve public health. Health is a national objective, but components such as population control, medical education, and drug control are under both the central and state governments. As such, constitutionally, the responsibility for health care lies with the state governments, while national health policy formulation and overall coordination of the work of the state health departments is managed by the Central Union Government.

Health Care System

The health care system of India is a mix of public and private sector. The public or the Government sector has three main levels: central, state and local. At the central level is the Ministry of Health and Family Welfare (IMHFWI), with the Directorate General of Health Services as the technical wing. The MHW is headed by a cabinet minister, and consists of the two departments of Health and Family Welfare. The Department of Health is headed by a Secretary to the Government of India while the Directorate General of Health Services acts as advisor to the Government on both medical and public health matters. At the national level, a Central Council of Health and Family Welfare was set up in 1952 to act as an advisory body and to consider and make recommendations concerning all aspects of health policy.

India consists of 29 states and seven union territories. In each state and union territory, a ministry of health headed by a minister looks after health and family welfare. All the states have established directorates of health, and some states also have separate directorates of medical education. Each state is divided into districts, which total 676 in 2014 in the country. The district is the principal unit of administration in India, and the districts vary widely in size and population. In each district there is a district hospital and a district health officer, who is in overall charge of all elements of district health administration. The district is divided into sub districts talukas, each with a community health centre or upgraded primary health centre. At the end of March 2012 there were 4,833 community health centres, 24,049 primary health centres, and 148,366 sub-centres. There are 23,236 PHCs functioning as on March 2012 in the country as compared to 23109 in September 2004. The total number of functioning subcentres for health facilities was 153,655 during 2015 (1). The primary health centres provide universally comprehensive health care services relevant to the actual needs and priorities of the communities at a cost which the people can afford. This includes preventive (vaccination, public health training, promotive (healthy health practices) and curative (medical-surgical services). Each primary health centre provides services for 20,000 to 30,000 people and is headed by a medical doctor. Under the primary health centres are the sub-centres, each of which covers a population of 3000 to 5000. Each Community health centre covers a population of 80,000 -1,00,000 and is spread over about 100 villages. A Medical Officer, Block Extension Educator, one female Health Assistant, a
compounder, a driver and laboratory technician look after the PHC. It is equipped with a jeep and necessary facilities to carry out small surgeries.

National health status indicators are shown in Table 1 (2-6).

Table 1: National Health Status Indicators

<table>
<thead>
<tr>
<th></th>
<th>1991</th>
<th>2012</th>
<th>2017</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population of India</td>
<td>846.302</td>
<td>1,220,200,000 (1.22 billion)</td>
<td>1,349,740,568 (1.34 billion) As of Oct. 14, 2017</td>
</tr>
<tr>
<td>Total male population</td>
<td>439.230</td>
<td>628,800,000 (628.8 million)</td>
<td>697,006,029 (697 million) (2017)</td>
</tr>
<tr>
<td>Total female population</td>
<td>407.072</td>
<td>591,400,000 (591.4 million)</td>
<td>652,734,538 (652 million) (2017)</td>
</tr>
<tr>
<td>Population growth rate</td>
<td>1.344 % (2011)</td>
<td>1.58%</td>
<td></td>
</tr>
<tr>
<td>Infant mortality rate</td>
<td>47.57</td>
<td>30.15 deaths/1,000 live births (2009 estimated)</td>
<td></td>
</tr>
<tr>
<td>Sex ratio</td>
<td>927 females per 1,000 males</td>
<td>940 females per 1,000 males</td>
<td>943 females per 1,000 males</td>
</tr>
<tr>
<td>Crude birth rate</td>
<td>20.97 births/1000 population (2011 est.)</td>
<td>21.4 births/1000 population (2013)</td>
<td></td>
</tr>
<tr>
<td>Crude death rate</td>
<td>7.48 deaths/1000 population (July 2011 est.)</td>
<td>7.0 deaths/1000 population (2013)</td>
<td></td>
</tr>
<tr>
<td>Density of population per sq. km</td>
<td>257</td>
<td>382</td>
<td>450 (2) (2017)</td>
</tr>
<tr>
<td>Proportion of urban population to total population</td>
<td>25.93</td>
<td>27.8</td>
<td>32.7 (3) (2011 Census)</td>
</tr>
<tr>
<td>Gross national product (Rs. in crores)</td>
<td>$4.16 Trillion PPP dollars, current prices- 2010</td>
<td>12034713 INR Tens of Million in 2016 (4) (8.594 trillion PPP dollars (2016) 99965.15 INR Billion in 2013 from 89328.92 INR Billion in 2012</td>
<td></td>
</tr>
<tr>
<td>Per capita expenditure on health and family welfare &amp; water supply &amp; sanitation (Rs.)</td>
<td>83.03</td>
<td>1312 Urban &amp; 332 Rural</td>
<td>US$ 59.10 in 2011</td>
</tr>
<tr>
<td>Literacy rate (%)</td>
<td>52.11</td>
<td>74.04 (2011) Male (82.14% &amp; Female (65.46%)</td>
<td>84.98% (6) in 2011</td>
</tr>
<tr>
<td>Work participation rate (%)</td>
<td>34.12</td>
<td>39.1% (2009)</td>
<td>Labor participation rate, male (% of male population ages 15+) in India was 80.70 as of 2011</td>
</tr>
<tr>
<td>Percentage of population below poverty line</td>
<td>29.9</td>
<td>Population below poverty line: 25% (2007 est.)</td>
<td>22% in 2011-12</td>
</tr>
</tbody>
</table>
As per information provided by Medical Council of India and Indian Nursing Council, the total number of registered doctors is 936,488 as on 31.12.2014, and as on 31.12.2013 auxiliary nurses/midwives are 756,937 & registered nurses/midwives are 1673,338. “As per the Report of the Steering Committee on Health for the 12th Five Year Plan of the Planning Commission, India has 19 health workers (doctors – 6, nurses & midwives – 13) per 10,000 people in India, WHO norms provide for 25 per 10,000 people. Additionally, there are 7.9 lakh AYUSH including Homeopathic practitioners registered in the country (approximately 6.5 per 10,000).”

**Evaluation**

Efficient evaluation of medical education requires the use of both internal and external agencies; neither can completely replace the other. Used together properly they enable the medical school to evaluate the complex and ever changing field of medical education in a fair and equitable manner first by the universities and then by Medical Council of India.

### Brief History of Medical Education

Medical education in India has existed since ancient times. The philosophy of Ayurveda (traditional Indian system of medicine, which takes into account the holistic nature of health, was predominant between 800 BC and 600 AD and spread in all directions to other Asian countries, including Thailand, Malaysia, Cambodia, Indonesia and Mongolia.

Ayurveda is a traditional Indian system of medicine whose name literally means “Life” (Ayuh) “Knowledge” (Veda); in other words, knowledge of life. The origin of Ayurveda dates back to the later part of the Vedic period (1000-500 B.C.). There are two well-known Ayurvedic treatises, one by Charaka Samhita (compendiums), a physician, and the other by Sushruta Samhita, a surgeon who lived near the first millennium B.C. (8th - 7th century B.C.) (7-11). Out of the four Vedas which are supposed to be the oldest books known to the library of mankind, the Atharvaveda contains descriptions about the various medical problems and the concept of health (12). The most fascinating contribution in Ayurveda relates to

<table>
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<th>Medical Education in India 182</th>
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<tr>
<td><strong>No. of medical colleges</strong></td>
</tr>
<tr>
<td><strong>In 2017, there were 479 Medical Colleges with admission capacity of 61,070 at undergraduate level. The total admission capacity for P.G. students is about 8684 in MS, 16195 in MD, 1280 in MCh, 1420 in DM and 3837 in various Diploma disciplines.</strong></td>
</tr>
<tr>
<td><strong>No. of hospitals/No. of beds in government hospitals (Including hospitals of local bodies)</strong></td>
</tr>
<tr>
<td><strong>35,416 hospital with 13,76,013 beds as on 14 August 2013 in Govt. Hospitals</strong></td>
</tr>
<tr>
<td><strong>Population served per bed</strong></td>
</tr>
<tr>
<td><strong>No. of sub-centres</strong></td>
</tr>
<tr>
<td><strong>No. of PHCs</strong></td>
</tr>
<tr>
<td><strong>No. of community health centres</strong></td>
</tr>
<tr>
<td><strong>No. of doctors (registered with MCI)</strong></td>
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</table>
understanding the phenomenology of disease. A systematic attempt was made to classify diseases into eight broad disciplines. It was also thought that diseases are the result of imbalance of the “humors”. Each disease was supposed to be influenced by a specific type of humor. Another interesting contribution of the Ayurveda was its knowledge regarding the relationship of diet and disease and on the role of environment (13).

The approach to training in Ayurveda was holistic and integrated. The state of health and disease is explained in this system based on the interplay of the constituent elements of the body: the general and alimentary regimen, and the influences of time and the season (13).

In the field of materia medica and pharmacy, the properties of drugs and foods were investigated. Diagnosis was to be made by the five senses, supplemented by interrogation. Diagnosis was based on cause (karankaran), premonitory indications (purva-rupa), symptoms (rupa), therapeutic tests (apace) and natural history of the development of the disease (samprapti).

According to Shusruta, the physician (chikitshak), the drug (dravya), the attendants or the nursing personnel (upasthata), and the patient (rogi) are the four pillars on which rests the success of the therapy. It was a very holistic approach.

The science of Ayurveda received its highest patronage from Buddhist kings (400-200 B.C.). With the spread of Buddhism to Asian countries, Ayurveda also spread to those countries and was adapted to the local needs.

**Siddha System**

The Siddha system of medicine is quite akin to the Ayurvedic, but is practiced more in southern India. It gives greater importance to the preparation of potions, syrups, and the like, from herbs with medicinal value.

**Unani Medicine**

Unani medicine is Greek in origin and was brought to India by Muslim rulers. It is still practiced in certain parts of northern India.

**Modern Medical Education**

The pattern of medical education is modeled after the British system, for obvious reasons of colonial influence. The early medical schools were established at Calcutta (1822), Bombay (1826), and Madras (1827) with the limited objective of training apprentices with minimum qualifications to help the army personnel. The first full-fledged medical college was established at Calcutta in 1838 under the supervision of the General Medical Council of Britain after 1860. The period between 1838 and 1916 witnessed the establishment of approximately nineteen medical colleges with an annual intake of 1,000 students. Following the passage of the Indian Medical Council Act of 1933, the Medical Council of India (MCI) came

### Table 2: Growth of Medical Education in Independent India (Allopathic System only)

<table>
<thead>
<tr>
<th>Period</th>
<th>Increase in Number of Medical Institutes</th>
<th>Increase in Enrollment</th>
</tr>
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<tbody>
<tr>
<td>1947 – 1965</td>
<td>17 – 87</td>
<td>1,400 – 5,387</td>
</tr>
<tr>
<td>1991- 2012</td>
<td>129 – 335</td>
<td>13,714 – 41,569</td>
</tr>
<tr>
<td>2015 – 2017</td>
<td>335-479</td>
<td>41,569 – 61,070</td>
</tr>
</tbody>
</table>
into existence in 1934 (14,15). Along with the establishment of Medical Colleges, another category of institution, offering three to four years of training, was established by the provincial governments, missions and private organizations. These institutions trained students for the degree of Licentiate Medical Practitioner (LMP). Though LMPs helped in overcoming the acute shortage of trained medical manpower in India, they were subject to criticism as imperfectly trained health workers and therefore the system was discontinued after independence.

The appointment of the Health Survey and Development Committee, popularly called the Bhore Committee (1946) was the first attempt to lay down a comprehensive blueprint of health service in India, in the quest for Indianization of modem medical education (16-18). The Committee laid foundations for the development of a national system of health care based on primary health centers. It recommended expansion of medical colleges, abolition of Licentiate courses, upgrading medical schools into Medical Colleges, suggesting measures to improve the quality of training, and the establishment of an All India Institute of Medical Sciences (AIIMS) (19). Following independence in 1947, and in pursuance of the recommendations of the Bhore Committee, India witnessed a phenomenal increase in the production of medical personnel (see Table 2).

However, in spite of this significant increase in the medical work force, the actual health needs of the people could not be satisfied as the distribution of doctors was erratic and irrational. For instance, the doctor - population ratio varies from state to state (from 1: 820 to 1:14015), with grossly unequal distribution between rural and urban areas (Table 3). The concentration of doctors in a few urban areas, the inadequacy and short supply of nurses and other health personnel, and the lack of relevance of training programmes to the actual health problems and needs of the population was a disturbing trend which resulted from the absence of a well planned health information system for regulating the development of human resources. The two major challenges for undergraduate medical education were therefore (i) to maintain standards and respond positively to modern concepts and methods in medical education, and (ii) to promote among graduates a sense of social responsibility and a spirit of dedication for serving the people, especially in rural areas. Unfortunately the infrastructure facilities in rural area are still very unsatisfactory.

Over the years, the government of India has appointed a number of committees and working groups to respond to these needs, Efforts to support and streamline the Indian medical education system have included the Health Survey and Planning Committee (Mudaliar Committee 1962) (20); the Committee on Multipurpose Workers under the Health and Family Planning programme (Kartar Singh Committee 1974) (21); the Group on Medical Education and Support Manpower (J. Shrivastav Committee 1975) (22); the Report of the Indian Council for Social Science Research - Indian Council for Medical Research (ICSSR-ICMR) Study Group (led by V Ramalingaswami

### Table 3: Total number of doctors

<table>
<thead>
<tr>
<th>Registered Doctors</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Modern Medicine</td>
<td>1.1.2015</td>
</tr>
<tr>
<td>Ayurveda</td>
<td>1.1.2015</td>
</tr>
<tr>
<td>Unani</td>
<td>1.1.2015</td>
</tr>
<tr>
<td>Siddha</td>
<td>1.1.2015</td>
</tr>
<tr>
<td>Homeopathy</td>
<td>1.1.2015</td>
</tr>
<tr>
<td>Naturopathy</td>
<td>1.1.2015</td>
</tr>
</tbody>
</table>
in 1981); the Adoption of the National Health Policy (1983) (23); the Medical Education Review Committee (Mehta Committee 1983)(24); working groups and planning commissions on medical education, training and manpower training; the National Policy on Education (1986) (25); and the Expert Committee on Health Manpower Planning, Production and Management (chaired by JS Bajaj 1987) (26, 27). More recently Niti Aayog has submitted a report to meet these challenges (28).

Reorientation of medical education (ROME) is a significant venture undertaken in India in collaboration with WHO SEARO with partial success. It was introduced in all the states of India in 1977 (29). Objectives of the ROME scheme are (i) to orient medical faculty, residents, interns and students to the conditions existing in rural communities and to provide training in the management of health problems encountered there; and (ii) to render comprehensive health care in the villages in collaboration with the concerned primary health centres. Accordingly, each medical college was to take on the responsibility for comprehensive health care in three community blocks (primary health centres) and was to gradually extend its coverage to the entire district. For this purpose, each medical college was to establish a well-knit rural referral system. Outreach activities, the posting of medical students in the community, the provision of mobile clinics, and the involvement of the entire faculty of the medical college were activities to be used for achieving the purpose of community based training.

The ROME Scheme has met with only partial success because of such factors as the lack of necessary infrastructure, logistics, the lukewarm attitude of medical faculty to participation in community based training, and the lack of concerted effort and institutional mechanisms for implementation. Moreover, neither a reward structure nor accountability and evaluation of ROME activities were part of the programme. On the positive side, some medical schools with effective leadership and faculty motivation have made significant progress towards community-oriented training (28).

Role of National Policy in Shaping Medical Education

The government of India instituted a National Health Policy in 1983 which was modified in 2002 emphasized that the effective delivery of health care services depended largely on the nature of the education and training received by the various categories of medical and health personnel, including its orientation towards community health, as well as on the capacity of the different types of health personnel to function in integrated teams, each member performing given tasks within a coordinated action programme (23,30). The National Health Policy reiterated that the entire basis of, and approach towards, medical and health education at all levels should be reviewed in terms of national needs and priorities. Curricula and training programmes were to be restructured (23,31) in order to produce personnel of various grades of skill and competence who are professionally equipped and socially motivated to effectively deal with day-to-day problems.

Towards this end, legislators believed it necessary to formulate a separate National Medical and Health Education Policy that (i) sets out the changes required in the curricular contents and training programmes for medical and health personnel of various levels of functioning; (ii) takes into account the need for establishing the extremely essential interrelations between functionaries of various grades; (iii) provides guidelines for the production of health personnel based on realistically assessed manpower requirements; (iv) seeks to resolve the existing sharp regional imbalances in availability of manpower; and (v) ensures that personnel at all levels are socially motivated toward rendering community health services.

The need for a national education policy in the health sciences was also expressed in the
reports of the Medical Education Review Committee in 1983 and the Expert Committee on Health Manpower, Planning, Production and Management in 1986 (24,25). The Committees brought into sharp focus the essential linkages between health and education policies, and emphasized that health planning and health services management should optimally interlock with the education and training of appropriate categories of health manpower through health related vocational courses.

The government of India is regularly reviewing the existing medical education policy to assess its strengths and weaknesses and give it a new direction, so that it has greater relevance and is more responsive to the national needs and health care system (31, 32). The emphasis is on balancing the availability of graduate and postgraduate doctors with their distribution (33-35). It has become necessary to correct the imbalance which has arisen and caused an over-abundance of many specialists and super specialists but a paucity of primary health care physicians. It is also necessary to control the increasing production of doctors (36-38).

As a part of this policy, the government of India in collaboration with the MCI has recently developed guidelines and regulations pertaining to the establishment of new medical colleges, the opening of higher cases of study, and greater control of the admission capacity of medical colleges (11). These guidelines also encompass objective assessment of the capabilities of medical institutions. It is envisaged that the MCI will assess both the desirability and the feasibility of starting new institutions, and will increase the number of courses in existing medical colleges. With this there is a shift in control from the state governments and universities to the federal government and the MCI. Some recent notifications like National Medical Commission Bill, which is awaiting Parliament approval is going to have far-reaching repercussion in different aspects of Medical Education and Health Care delivery in India.

**Demographic Profile of Medical Undergraduates and Faculty**

**Regulations of the Medical Council of India**

Regulations of the MCI require that, for admission to medical college, a candidate should be at least 17 years of age and should have passed the Higher Secondary qualifying examination, or the equivalent, held after 12 years of schooling (34-39). Most states have adopted a 10 plus 2 pattern of education, which means 10 years of secondary and two years of higher secondary education, which latter should include physics, chemistry, biology and mathematics or any other elective subject with English as the core subject. A candidate seeking admission to an MBBS course must have passed the qualifying examinations with a minimum of 50 per cent aggregate marks in English, physics, chemistry and biology.

Selection of students by medical colleges is based solely on the merit of the candidate. In states with only one medical college, the marks obtained in the qualifying examinations are used as the basis for admission. In states, where more than one university/examining body conducts qualifying examinations, an additional competitive entrance examination is held. The All India Institute of Medical Sciences (AIIMS) has its own multiple-choice entrance examination. Most states also have a residency requirement for admission to 75 per cent of the places, although in institutions such as AIIMS, all seats are open to candidates from all states and union territories. The Government in 1987 introduced an All India Entrance Examination to be used as the basis for selecting 15 per cent of candidates for each government medical college, and each medical school must reserve 15 per cent of its places for students from this national merit exam list. Thus, 15 per cent of students usually come from states other than that in which they study while 85 per cent live in the state in which they study. The Council has also established the minimum requirement for admission to medical college as 50 per cent aggregate marks in English, physics, chemistry
and biology, although this requirement is under review and, for candidates belonging to scheduled castes/scheduled tribes, the minimum aggregate marks required are 40 per cent. The Indian constitution guarantees that educational institutions will reserve places for applicants from specific scheduled castes and scheduled tribes that have traditionally lacked such opportunities. Recently (since 2016) the MCI has introduced an all India entrance examination for all seats of MBBS in all medical colleges to have uniformity and convenience to the students, called Undergraduate National Entrance and Eligibility Test (UG-NEET) conducted by the Central Board of Secondary Education (CBSE), New Delhi.

Certain self-financing non-government colleges admit 15 to 25 per cent students on merit as well as on donation as agreed by the Government. These institutions are run by private trusts or by societies and are not entitled to receive government grants. These private medical colleges could adopt their own fee structure and charge capitation fees. However, the charging of capitation fees has recently been banned by the Supreme Court of India while the fee structure is now controlled by the Government and varies from state to state. The fee structure also varies widely between private medical colleges and government institutions.

**Trends over the Years**

A detailed demographic profile of medical students and medical faculty is not available. However, the general trend, as evidenced by the large number of applicants every year, is that medical school admission and a medical career is becoming more and more coveted. All increasing number of candidates belongs to the upper middle classes and more and more students whose parents are educated and employed in urban settings find places in medical school but there is also increasing number of Schedule Caste and Schedule Tribes students joining the medical college during the last two to three decades.

**Guidelines by the Medical Council of India for Teachers**

The MCI, as a national regulating body, lays down standards regarding the number of faculty for each discipline and the minimum qualifications and experience required for teachers at different levels. To be eligible for the lowest teaching positions (lecturer/assistant professor) in a medical college, a teacher must have a postgraduate qualification (MD/MS) as well as a graduate qualification (MBBS) and a minimum of three years experience as a registrar/senior resident.

To be eligible for a professorship, a teacher must have a minimum of ten years experience after obtaining an MD or MS, of which at least five years must be at assistant professor level or above. There are some variations in different universities, but each medical college must fulfill the minimum eligibility criteria. Recently the MCI has also included necessary research experience with research publications as eligibility criteria for teachers in their promotion. There is a dictum that when numbers increase the average tend to fall. Hence, there is decline in the standard of teachers.

**Undergraduate Curriculum and Innovations**

**Description of Existing Curriculum**

The nature of the medical curriculum falls within the purview of the MCI, which prescribes the curriculum, lays down procedures for admission and patterns of examinations and regulates the minimum requirements for physical space, equipment, staffing patterns, etc. While the Council sets down broad principles and minimum requirements, the details are left to the universities and colleges.

The medical course consists of four and a half years of undergraduate study followed by a one year compulsory rotating internship. The curriculum is discipline-based. The first 18 months (known as Phase I) includes the preclinical subjects of anatomy, human
physiology and biochemistry (15 months) and an introduction to perspectives of medical education (3 months). Phase II covers clinical subjects, and is taught over a period of 18 months. This course consists of pathology, microbiology, pharmacology, forensic medicine, and community medicine. Phase III, the continuation along with the study of paraclinical subjects, consists of medicine, surgery including orthopedics, obstetrics and gynecology, pediatrics including social pediatrics and eye and ENT (ear, nose and throat), and a community medicine posting.

Clinical postings begin in the Phase II years, i.e. after one and a half years of preclinical studies, and students are posted for not less than three hours per day. University examinations are usually held at the end of the preclinical and para-clinical phases. The examination for the clinical phase is held in two parts, the first consisting of community medicine, ophthalmology and ear, nose and throat; and the second part consisting of medicine, surgery, and obstetrics and gynecology. The examination includes theory and practical elements as well as an assessment for each student by the medical college teachers which accounts for approximately 10 per cent of the total marks.

After passing the MBBS examinations, candidates are granted provisional registration for one year, during which time they undergo a compulsory rotating internship. The internship is fulfilled in teaching and approved hospitals such as district hospitals and rural health training centres or upgraded primary health centres attached to training institutions. The internship includes hospital training for six months in medicine, surgery, and obstetrics and gynecology; and training for six months in community health work in an appropriate health centre, which also includes in-service training in family planning clinics for one month. The Council provides for training in any elective clinical subject such as pediatrics, ophthalmology, otolaryngology, dermatology, psychiatry.

There is no structured curriculum for the training and evaluation of interns. However, broad guidelines have been provided by the MCI (39,40). The intern maintains a record of work that is verified and certified by the medical officer under whom he/she works. Based on the record of work, the dean of a medical college will issue a certificate of satisfactory completion of training, after which the university awards the MBBS degree. Full registration is given by the State Medical Council on the award of the MBBS degree by the university. The universities that medical colleges are affiliated to are responsible only for conducting examinations and awarding degrees.

Objective of Graduate Medical Education

The MCI has emphasized the objective of producing medical graduates who are capable of functioning independently and effectively in both rural and urban settings. The importance of social factors in relation to health and disease, the teaching of health education, the need for stressing population control and family planning, and the provision of teaching opportunities in outpatient departments, emergency departments, and community settings have all been highlighted (39).

Though a discipline-based curriculum has been suggested, the council has recognized the need, through the practice of integrated teaching, to reduce artificial compartmentalization of the curriculum into preclinical, para-clinical and clinical disciplines. For this purpose, the Council has recommended interdepartmental integrated teaching-learning activities. The MCI has recommended that a mechanism be established to promote both horizontal and vertical integration among the preclinical, para-clinical and clinical disciplines, but this recommendation has not yet been instituted in most medical colleges. Regarding the method of instruction, MCI favors reducing the amount of didactic teaching and increasing participation in such activities as small group discussions and seminars. Traditionally, however, instruction in
medical schools has been teacher-oriented rather than learner oriented, and attempts to reverse this trend have been limited to a handful of medical schools. The paucity of innovative approaches is attributed mainly to inadequate opportunities for teacher training and orientation, lack of incentive structures to recognize and reward the teaching effort, and preoccupation with patient care or research as a preferred activity.

Analysis of Strengths and Weaknesses of the Present System

Certain deficiencies need to be addressed when launching curricular innovations. Currently in India, teaching is not aligned with the morbidly pattern prevalent in the primary health care setting, and it is alleged that the topics of rare diseases and complicated cases take precedence over the topics of common interest that have great relevance to the public health situation. Although community health problems prevalent in India are covered in the syllabus for undergraduate medical education, instruction in, and evaluation of, these aspects of medicine are not adequately emphasized.

Other inadequacies in the medical school curriculum induce the fact that the activities and skills expected of a primary care physician, such as communication and managerial skills, working as a member of health team, rational drug therapy, and cost-effective interventions, are not addressed. As well, the sites of training, being predominantly hospital based, are not congenial for training in primary care.

While the level of knowledge in the medical sciences is highly satisfactory, medical graduates are often found to be lacking in the skills required for patient management, especially in regard to common emergencies. Development of communication skills and attitudes, including ethical and humanistic attitudes, is yet another area of concern, while the need for the introduction of psychological and social aspects of health and disease possibly through courses in behavioral sciences is keenly felt. The assessment system in vogue is held to be a main culprit of the shortcomings of medical graduates, as it tests recall of information rather than the ability to analyze facts, interpret data and arrive at conclusions regarding the meaningful application of knowledge gained for solving the real problems of the individual and the community. The greatest challenge for medical education in India, therefore, is to design a system that is deeply rooted in the scientific method and yet is profoundly influenced by the local health problems and by the social, cultural and economic settings in which they arise.

So far in India, attempts to introduce innovations into the curriculum have been limited to certain institutions, and sometimes even to individual departments of an institution. Nevertheless, these isolated and modest attempts to reflect an increasing awareness of the needs of modern medical education and the perseverance required to swim against the current.

Staff Development

One of the serious deficiencies of medical education in India, as in many other countries, is the lack of adequate motivation and opportunities for faculty development, which results in indifference to research in teaching and education. While medical teachers may be highly efficient professionals in their respective branches of specialization, they display a kind of amateurism in the role of educator. This might be because of the fact that teaching efforts are not rewarded or even considered a desirable criterion for selection or promotion compared with clinical skills or contributions to research in the medical sciences. It is for this reason that innovative approaches to curriculum planning, instructional design and application of educational technology have not received much stimulus in the past. However, there are reasons to believe that the trend is shifting. Recently, emphasis has been placed on faculty
development by the education policy on health sciences, and MCI is also taking a fresh look at faculty development. It is therefore likely that a significant impact on faculty development and research in medical education will be felt. However, National Academy of Medical Sciences (India), an autonomous organization under the Ministry of Health and Family Welfare (MoHFW) has been entrusted by the MoHFW to undertake continuing medical education (CME) programmes not only to enhance and updating the knowledge and skills of medical teachers and practicing health professionals but also to undertake research activities in medical education in the country (41).

Besides, at present, there are few National Teacher Training Centres (NTTCs) - in Pondicherry, Varanasi and Chandigarh. There is also a Centre for Medical Education and Technology (CMET) at AIIMS, New Delhi, and approximately a dozen other medical education units are attached to medical schools which are actively engaged in medical education activities. With the establishment of new universities in health sciences, in many states, a few more regional centres are expected to appear in the near future (42,43).

A group of medical schools in the country led by the four leading institutes - AIIMS, New Delhi, Institute of Medicine, Banaras Hindu University (BHU), Varanasi, Christian Medical College, Vellore and Jawaharlal Institute of Postgraduate Medical Education and Research (JIPMER), Pondicherry - have organized a national Network for undertaking innovative projects in medical education. Currently there are twenty medical colleges which are members of this Consortium and it is planned to conduct Advance Courses on Fellowship in Medical Education (FIME) with the purpose of developing educational practitioners who can lead educational changes in their institution to make medical education responsive to the health needs of the country. Presently, ten Nodal Centres have been recognized by the MCI for this purpose (42, 43).

Teaching the Teacher to Teach (Training of Trainers)

Medical educationists agree that medical teachers need to be taught the methods and science of education. This should be made compulsory but is still an option. This approach should be inquiry driven and help in improving the teaching and technical skills. The efficiency and effectiveness of medical education will be influenced by incorporating these changes (42-44).

Role of the Government and Private Sectors

Traditionally, the Indian medical education system has been scarcely influenced by the private sector. However, of late there has been fresh thinking to encourage private initiative and investment, particularly in view of current resource constraints, provided the initiatives satisfy the minimum standards. However, with the sudden increase in the number of Private Medical Colleges, the quality of education is falling. While this has reduced the financial pressure on the government, it has also promoted a high technology culture, with excessive reliance on technology-oriented diagnostic tools / and techniques, making health care more expensive.

India is a signatory to the goal of Health for All and as such the production of physicians who are able to play their roles effectively as leaders of the health team in providing comprehensive primary health care is considered important in medical training. The points of view earlier raised at the Edinburgh Declaration of the World Federation for Medical Education (WFME) have been fully endorsed at the national level (44-46).

Issues and Trends (and Predictions)

The need to redefine Goals

The need to redefine goals of medical education is unequivocal and imperative. Such revision should be based upon careful study of
a) The health needs of society,
b) Philosophy of scientific thinking,
c) The professional characteristics of physicians.

Traditionally, education for any profession has been designed to

i) Recruit adequate numbers of qualified students,

ii) Educate and train them in the necessary areas of knowledge and application of that knowledge along with the skills and attitudes required,

iii) Certify for public protection and successful practice of that profession.

Further, health care needs of society are not static and are different for different societies and have remarkably changed within each society. Secondly, as new scientific knowledge is generated with concomitant growth of technology, so medical education grows longer in duration and more expensive. The apparent response of medical educators to these remarkable accreditations of knowledge to add them to the already overcrowded medical curriculum is not always smooth.

Shortage of medical and health care manpower might be no more than incorrect utilization of presently available manpower and inadequate understanding of health personnel needs. Significant patterns of delivery of health care have also changed over the last few decades and the goals of medical education surely must reflect these changes. The growth in communication technology has also greatly influenced the rapid advancement of scientific knowledge but also its application with democratization process. It has also changed the expectations of patients.

Some major initiatives that have taken place recently include suggestions for the planned constitution of a Medical Education Commission and recent attempts by MCI to design a needs-based curriculum. As well, a Consortium of Health Institutions involving the AIIMS, New Delhi, the Institute of Medical Sciences, BHU, Varanasi, JIPMER, Pondicherry, and the Christian Medical College, Vellore, in collaboration with the Department of medical Education, University of Illinois, Chicago, USA, has been established to spearhead the reorientation of medical education.

Thus, at present, medical education in India is at a significant juncture. With initiatives coming from both external and internal influences, and the political will to attain the goal of health for all, India hopes to be in a better position to mould physicians entering the twenty-first century. Although the Medical Education Commission constituted, it is expected to assume a three-fold function of analyzing the needs of education in medical health sciences, deciding a pattern of financing the same and establishing mechanisms of coordination among different professional councils and other bodies.

Well defined, broad-based revision of the rules and regulations governing undergraduate and postgraduate education is currently being undertaken by the Medical Council of India. This will help every medical school to improve training and teaching. After the dissolution of the Medical Council of India, the National Medical Commission will guide the medical education and health care in India.

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Medical Research by the Medical Colleges in India

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ABSTRACT

Background: Research conducted in medical colleges in India is often considered to be of poor quality. The study was done to assess the cause for such occurrence.

Materials and Methods: Papers published in indexed journals between 1985 to 2017 were reviewed and the data was synthesized.

Results: Poor infrastructure, heavy patient load, restricted number of faculties who had limited exposure to research methodologies, private practice, lack of incentive to do good quality research, poor mentoring, lack of research tradition, research fund, ancillary infrastructures, and copy cat research were found to be some of the reasons.

Discussions and Solutions: Teachers education, provision of better infrastructure and funding, short term fellowships at both undergraduate and postgraduate levels, proper assessment for promotion of teachers, training in research methodology, multicentric research, R & D research bases in medical colleges, looking for solutions for day-to-day challenges through operational and translational mode are some of the solutions. Training from undergraduate levels on elements of research needed to be encouraged.

Keywords: UG medical student, training, research methodology challenges, teachers education.

Situational Analysis

There are more than 450 medical colleges in India churning out around 60000 medical graduates per year. Out of these, 50%, i.e. 30,000 graduates do various types of postgraduation or superspecialisation. This does not include parallel DNB examination at the specialization / superspecialisation level. Hence it may be assumed that as per Medical Council of India (MCI) requirement these 30,000 postgraduates / superspecialists (MD/ MS/ DM /MCh) are submitting so many dissertations every year. How good are these dissertations. One of the ways to assess the quality of these theses is to ask the authors, what they feel about it. Our experience is that students hardly feel any attachment to their theses and less than 10% of such dissertations are eventually published as full papers in any of the national indexed journals. There are a handful of medical colleges where sufficient interest is shown by the faculty in mentoring the postgraduates and reasonably good publications come out of from a few students from these handful of medical colleges.

Biomedical research of some quality is conducted by independent research.
organizations or their Institutes like Indian Council of Medical Research (ICMR), Council of Scientific and Industrial Research (CSIR), Department of Biotechnology (DBT), Indian Institute of Sciences (IISc), etc. to name a few. Even from these organizations and Institutes, real collaborations with medical colleges are few and far between. Hence many of the important day-to-day challenges which the doctors in medical colleges and other hospitals are facing do not find an echo in the nature of research done by the august organizations leading to a disconnect between the requirement and the product. Since 1990s several scathing criticisms on the nature of research in medical colleges in India has been published (1-5). In those articles not only poor quality of research but academic dishonesty, poor output of research paper were also highlighted. A review of that time (1) analyzing 128 medical colleges commented only top 6 college published 56% of total research papers. We would like to see what could be possible reasons for such an affair and whether something can be done about it.

**Mediocrity Rules the Roost**

To mentor a student for research we need good mentors. However, at the medical college level majority of the teachers are not well versed with science and art of medical research. Methodology, how to find out the problem, how to devise a study, analyzing the ethical component and address them and finally conducting the study are the important components of medical research. Like in many areas of education medical education in India in many ways are incomplete. Churning out large number of doctors with bare minimum training and finally inducting them as teachers in those medical colleges are a few reasons for such mediocrity in research.

**Lack of Incentives**

There are no incentives for good research work. Promotions require that faculties at different levels when considered should have at least one, two or few publications. But MCI does not specify what sort of publications is to be counted, at what level of authorship? How many students are mentored, what these students eventually produced? What other engagement should also be considered as research-related engagement, i.e. peer reviewer of good journals, members of project review committee constituted by funding agencies, assessor of PhD level research from good institutions, engagement in community-based research activity etc. In fact, faculties across the country in medical colleges are regularly promoted without a track record of mentoring or doing research. What to talk about faculty in medical colleges, private and government medical colleges are running with contributions from ghost faculty who comes during MCI inspection and then is heard no more.

In case of government medical colleges authorities assemble faculty from other colleges or temporarily transfers faculty from other colleges to tide over the crisis of MCI inspection for adequate infrastructure and faculty. Modern era of pay and publish your research also destroyed whatever little credibility of medical college faculties had by publishing something in local medical journals and using them for their promotion.

**Private Practice is the Be All and End All Motto**

How can a medical faculty in a medical college give time to his students for training and research when he is always looking at his watch when to leave the premises for private practice. It is difficult to blame the faculty entirely for such a state of affairs because they are not always paid well, they don't have other amenities which a good medical college should have provided and even many families looks at the doctor for earning adequate money for the extended family. Private medical colleges are not cheap, many teachers who came from such colleges have a huge debt burden to be paid for by their earning. Society also now-a-days do not look with respect
to a doctor who is dedicated to his college and do not earn extra dime through private practice.

One is not surprised that now-a-days to see private clinics running upto midnight, how then this doctor will come to the medical college next day morning, see patients, teach both undergraduate and postgraduate students, mentor his postgraduates for research and finally do his own research? In fact Reddy et al (2) blames private practice as the major cause of poor research performance by medical colleges in India.

### Huge Patient Load

Every hospital particularly Government medical colleges and some very good private medical colleges have extremely high patient load and it is often physically impossible to give attention to all the patients that attend these centres. The faculty and junior doctors in our country day in and day out face such overwhelming crowd of distressed humanity. Hardly they can spend more than a minute or two with each patients. Though this improves their clinical skills (do they ?) this does not produce an ideal environment for patient-based research, which medical colleges are supposed to do. Hence crowd management rather than proper patient management takes the front seat and research can be seen nowhere. We often speak of our patient load, a golden opportunity to do good quality clinical research but their humongous number itself prevents such an enterprise to take root.

### Extremely Poor Infrastructure in Medical Colleges

Most of the medical colleges in India has extremely poor infrastructure. Many of the modern investigations which are required for day-to-day patient care often needs to be outsourced. This can easily be seen when one moves outside the medical college campus and sees proliferation of private laboratories to cater for the patients. Many of these laboratories are now famous laboratory chains across the length and breadth of the country. While patient care somehow can be managed with this approach training and research in medical colleges suffer. Most of the medical colleges also do not employ medical statistician and the case files in many colleges are poorly written, cursory and incomplete so also the hospital record section.

Many hospital-based research, particularly retrospective research is dependent on good quality medical records and its proper archiving, which is sadly lacking in most of the medical institutions in India. Experimental studies which requires laboratory animal facility has also vanished from majority of the medical colleges in the country, or it was never constructed in many newer medical colleges. Medical colleges also have no special funds to carry out research. It is extremely sad that from each of these medical colleges, each year so many doctors are coming out, many of them become successful medical practitioners, earn lots of money but donate next to nothing to their alma mater. This is in contrast to IITs in India. In fact personal donations should have produced huge corpus in each of these colleges to drive research. For example if out of the 60,000 medical graduates produced by the country even if 10% of them becomes successful medical practitioners then we are talking of 6000 successful doctors each year and they donate only once in their life a sum of 100,000 rupees then 6,000X100,000, i.e. 60 crore rupees of personal donation should flow each year to these medical colleges and in the span of 30 years we could have 1800 crore rupees of personal donation meaning thereby a corpus of at least 4-6 crore rupees to each of the medical college in India to drive research.

### Copy Cat Research

Many dissertations and research projects written are basically copycat research. While there is no harm if copy cat research improves our health care infrastructure and our students understanding how good research can be
conducted. But 100% copycat researches eventually do not bring any original thinking, meet the local medical needs or successfully face the research challenges in the country. This has been highlighted in detail by Arunachalam (6).

Lack of Collaborative Research Activities

Now-a-days many good research emanates from joint, multicentric research. It seems in our country we are incapable of doing collaborative research except few examples, whereas in international arena often hundreds of medical centres take part with a common research goal. Such kind of research easily attracts attention because of its sheer size, brings about statistically robust facts. It can be seen the mega trials which brought aspirin in the secondary prevention of ischemic heart diseases would have been possible without several of those mega trials. Those trials are not difficult but time consuming to the trialists.

Inadequate Follow-up

This is one of the biggest problem which conspires against conducting good quality research in our country. Without blaming patients, doctors, institutions and the facilities it can be said our patients do not understand the need to come back for follow-up to the doctor to say that I am well or I did not get well with whatever was prescribed. This lack of follow-up not only hampers research but more than that the doctors does not come to know that whatever he prescribed worked or not, hence he loses one of the most important avenues of continuous medical education. Probably patient feels I am alright with his medicine hence why should I go back to him or his medicine did no good what is the point in going back to him. In both ways patient also becomes a loser, for diseases like tuberculosis patient feels better within 2-3 weeks of therapy and stops medicine, does not go back to his doctor. Had he done that doctor would have told him to continue the medicine. This results in emergence of multidrug- and extensively drug-resistant tuberculosis (M/XDR-TB), relapse in the patient, more costly and eventually less successful intervention. Part of this non follow-up could be financial but partly this is in our national persona.

Funding Agencies

In India, several government funding agencies fund medical research. These agencies are ICMR, DBT, Department of Science and Technology (DST), CSIR, Board of Research in Nuclear Sciences (BRNS), etc. Unfortunately many private industries which could have put up some fund for research are nowhere to be seen. If one concentrates and see the funding pattern from these organizations, it will be apparent that 15-20 institutes/medical colleges in this country corner 70% of the funds available for adhoc projects. The reasons for this are many and one of them is of course the few successful institutions write better quality projects but other reasons will not be very palatable to the funding agencies. Recently each state has developed their modest research funding patterns and ICMR has given substantial funds to almost 100 medical colleges in the country for improving research atmosphere in those colleges. ICMR/DBT is also individually funding students at undergraduate / postgraduate levels to do project or thesis work. However, number of such grants are less and amount is also insufficient.

Recently three national science academies in the country together are encouraging faculties from different colleges to spend some time as summer trainees to some of the centres of excellence to develop some ideas related to developing research protocols in their home institutions. All research funding organizations are also spending 10% of their budget to stimulate research activities and develop research infrastructures in North Eastern states of India.

However, all these measures are recent and we have to see whether these interventions make any difference in research activities in these institutions in future.
R&D of Pharmaceutical Industries and its Co-ordination with Nearby Medical Colleges

India has one of the biggest pharmaceutical industries in the world, barring few, yet R&D, in these industries are meager. If majority of these pharmaceutical industries could open a collaborative R&D centre in various medical colleges it will be a win-win situation. In olden days, Burroughs Wellcome used to have such R&D centres in RG Kar Medical College, Kolkata and in CMC, Vellore. This kind of centres depending on the particular company's strength can generate interest in different areas of biomedical research in the country. Department of Health Research (DHR), Government of India is supposed to see that this kind of collaborations happen in a grand scale. In addition we have a tremendous traditional medicine heritage at the level of medical colleges Ayurveda, Yoga, Unani, Siddha and Homeopathy (AYUSH)/DHR/ICMR/Central Council for Research in Homeopathy (CCRH) can harness collaborative research to bring out the best and popularize the use of such medical approaches for common ailments. As an example, studies in modern institutions funded by ICMR has shown Ksharasutra method of treatment for anal fistula is better than classical surgical technique. But have we popularized its use? The answer is no. As a result of this, current generation of surgeons may not have even heard the name Ksharasutra.

This kind of collaboration to a large extent also will bring necessary funds for research in a medical college. This will also end total apathy due to ignorance of modern medical doctors to the gems of ancient Indian knowledge in medicine.

Hindrances in Randomised Control Trials

Randomised control trials (RCTs) may not bring basic research in medical colleges but being a part of it teaches faculty of a medical college the rigor of doing a good clinical research. This kind of research brings good amount of money to the organization and brings national and international fame to the medical colleges. There are rules and regulations to make such trials safe (as much as it can be) to the volunteer patients for this trial. However, the rules and regulations for giving this trial in this country has become so tight and getting permission to do the trial are so time consuming that the very idea to conduct an RCTs in India immediately brings negative feeling. While we must agree to tighten all the norms for the purpose of safety, yet we should not tighten it to such a degree that no worthwhile trial can be stopped.

MCI Needs to Revamp its Curricula/Syllabus for Medical Education

In modern era there is a need to revamp medical syllabus. Lots of clinical research done in India is not studied by our postgraduates as they mainly study international books. Modern research needs basic scientists in addition to doctors. AIIMS has research scientists post at various departments. Prof. Karmarkar without being a medico became Professor of Medicine in AIIMS. MCI must at least create adjunct faculty/adjunct professor post to improve research in medical colleges. These adjunct professors could be from a general college, engineering college, and research institutions. There should be stricter norms for considering a paper for promotion. Other elements of research activity also needs to be considered.

Research is not Divorced from day-to-day Practice

One of the major problems in modern medical teaching in India is that research has not been any priority and it has been made to appear that research is really divorced from our day-to-day medical practice, which is not. All our medical teaching including bedside teaching, particularly needs to focus on that.

Basically such type of orientation should start from undergraduate levels. Several
examples can be given, e.g. if you take 10 patients of myocardial infarction and look into details their clinical presentations, all ten will be different, we may not know all the reasons but a student should have the inquisitiveness to enquire why ten fellows are presenting differently, i.e. some with epigastric discomfort, some with profuse diaphoresis, some with pain in the hand and some with pain in the jaw, etc.

**Quality of Teaching and Teachers in Medical Colleges**

Good quality and number of researches can come out of the medical colleges only if the college has good and proper teaching credential. Poor teaching and lack of adequate faculty in many medical colleges has been pointed out by early workers (7-9). Some of them also have pointed this out in their inimitable writing style (10). We present many research papers in our different annual conferences and very few of them are eventually published. Quite often these abstracts are prepared by postgraduates but lacking in final push it does not see the light of the day in the form of a valid publication (11). Though postgraduate students are supposed to do research in the form of dissertations (12), they often not properly mentored by their guide. There could be different reasons for such a lacunae. Moreover teachers of medical colleges who are usually the guide hardly have any time for mentoring. Many of them are not also qualified to do so because they lack education and training in that area. Some Institutes do have research methodology course which must be undertaken by PG students but this is not universal. Hence the PG students who are the future teachers of the country grow up in cut and paste mode without learning any elementary principles of modern medical research.

**Examples of Medical Institutions doing Good Quality Research**

Solutions to improve research capabilities in the medical colleges in India can come from taking examples from those medical colleges which are already known to be in the forefront of medical research in the country. For example institutions like PGIMER, Chandigarh, AIIMS, New Delhi, SGPGI, Lucknow are known to be regularly producing good quality research article. These government medical colleges are reasonably well funded. The faculties from these institutes are well represented as experts and reviewers of most of the Government funding agencies and these institutes discourage private practice, however the salary of the doctors are some of the best in the country and they all can take the advantage of institutes accommodation. The selection procedure for the faculty is tough and there are no regular avenues of promotion as well as chances for them to go abroad for a period of two years to get a fruitful academic experience besides of course and earn far from ideal extra money. In addition these institutes have developed programmes with some of the best western Institutes to carry on high quality research. In some of these organizations a strong assistance from non-medical scientists cadre exist and unusual departments like department of experimental medicine in PGIMER, Chandigarh cooperating with other clinical departments for doing research. We also have medical colleges like KEM Hospital, Mumbai where reasonably good quality research goes on even though the faculty members practice outside and they do not have many of the facilities of the above mentioned colleges, hence in many ways this institute resembles most of the other medical colleges in India. Moreover being in the hub of financial capital of India, there are lots of reason for the faculties to get distracted from research. This institute also has a long research culture in having their own research society and there are many ICMR research centres and other research institutions around this medical college which definitely helps KEM Hospital in developing many collaborative research work. Then there are premier medical college-cum-research organization like CMC Vellore where both national and international collaboration and research programme brings money, projects and good name to the institute and here also no private practice is allowed.
Solutions

So how we can make medical college faculties to get engaged in good quality research programmes? First the faculty should feel an urge to do research and this starts from when a future faculty as an MD student writes his / her dissertation. If his boss is exacting he can learn the elements of medical research from him. Now-a-days research methodology course has been started for postgraduate medical students, this could be made universal and interesting. Faculties should be rewarded for publishing good quality research papers or bringing competitively funded project to the college or when they are selected in peer review committees of national or international funding agencies. If any nearby good non-medical research institution is there, the faculty should try to tie up with them to produce good project. ICMR in an effort to start good research in medical colleges have already started funding small ICMR research units across the country with instrument and manpower support. The administrators of state medical colleges must understand that modern medicine is progressing in such a way that many departments in a medical college are in need of non-medical scientists, hence a cadre of non-medical biological scientists needs to be created for different departments of medical colleges to suit the needs of individual departments. Several authors suggested a number of solutions to address this problem, i.e. mentoring, research-oriented medical education, short-term student funding at undergraduate and postgraduate levels, workshops, hand-holding by good research organizations, improving the quality of the faculty, reducing the patient load and teaching some of the Indian medical research finding in the curricula (13-17). In the MBBS curricula, the only subject where how to do medical research is taught in a very elementary way is Preventive and Social Medicine (Community Medicine). However, MBBS students pay little interest to this subject. This subject should be made more interesting. In some universities, an additional BSc (Hons) degree is given if a candidate takes one year extra to do some quality research in any of the subjects being taught in MBBS level. This could be difficult in this country but similar programme which are student friendly could be initiated.

Now that the study of medical scientometry (18) is with us and many of the medical journals are internationally indexed as well as we have our own indexing agencies; it is unlikely that like previous decades our research work will be lost to the international community, only we have to conduct good quality, locally-relevant research for our country.

Conflict of Interest

None.

Acknowledgement

None.

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Clinical and Experimental Studies in Japanese Encephalitis: Lessons Learnt

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ABSTRACT

Introduction: Managing encephalitis for last 3 decades and conducting experimental studies have provided a number of important findings some which are presented.

Method: Summary of important clinical, radiological, neurophysiological and biochemical studies are presented. The results of experimental studies in a rat model have been used to investigate the basis of behavioral changes, histology, and molecular alterations in Japanese encephalitis (JE) and finally an approach to acute encephalitis syndrome (AES) is presented.

Result: The patients with encephalitis can be produced by a number of noninfectious, infectious. The local prevalence and time of the year are crucial for clinical decision making. The affinity of JEV for thalamus, corpus striatum, substantia nigra, cerebellum and anterior horn cell was documented by imaging studies, which was further confirmed on immune histopathological and real time PCR studies highlighting the tropism of JEV. The lower motor neuron involvement on EMG studies was attributed to anterior horn cell involvement. JE results in frequent and severe movement disorders. The basis of movement disorders was revealed in MRI and SPECT studies showing thalamic and cortical hyperperfusion suggesting the involvement of thalamo-cortical projections. Hyperkinetic or hypokinetic movement disorders were due to differential involvement of excitatory or inhibitory circuits in the brain. Reduction in catecholamine and its metabolites in CSF of patients was supported by reduction of catecholamine and dopamine receptors in the JE tropic areas in thalamus, corpus striatum and brainstem resulting in dopamine deficiency. The learning and memory deficits in JE were attributed to cholinergic dysfunction revealed by expression of CHAT, HQNB CHR M2 mscarcin receptors in the JE affected areas of brain.

A syndromic approach to AES categorizing the patients into neurologic or systemic group and using rational investigations; imaging and Acyclovir therapy in pure neurologic group and avoiding these in systemic group is recommended. In systemic group, treatment with doxycycline for scrub typhus, artesunate for malaria, ceftriaxone for leptospira and fluid management for dengue are recommended.

Conclusion: A combined clinical and experimental approach provides valuable information to understand the basis of clinical alterations in JE.

Keywords: Japanese Encephalitis, herpes simplex, dengue, chikungunya, syndromic approach, clinical MRI.

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DR. BALDEV SINGH ORATION delivered during NAMSCON 2017 at Sri Guru Ram Das Institute of Medical Sciences & Research, Sri Amritsar, Punjab.
Introduction

Acute Encephalitis is a global health problem with diverse etiologies. A number of non-infectious conditions (mitochondrial disease, autoimmune encephalitis, cerebral venous sinus thrombosis) and non-viral infection (bacterial or fungal parasitic) may simulate viral encephalitis. Over 100 neurotropic viruses can also result in the syndrome of Acute Encephalitis Syndrome (AES). AES is defined as fever with altered sensorium with or without focal sign of seizures or evidence of raised intracranial pressure after excluding febrile convulsions. The etiology of AES varies according to the geography and season because of difference in the prevalence of organisms and their vectors. Herpes simplex encephalitis (HSE) to the commonest focal encephalitis, which does not have a regional or seasonal preference. Geographically restricted encephalitis is mainly arthropod borne. The commonest endemic viral encephalitis in south east Asia in Japanese encephalitis (JE). West Nile, Chikungunya and Nipah viral encephalitis are also reported from Asia. Murray valley encephalitis, JE and Dengue are reported from Australia; West Nile from middle east, Tick borne encephalitis in Russia and West Nile, St Louise encephalitis have been being reported from America (1). In tropical region, malaria pyogenic meningitis are common and Scrub typhus outbreaks have been reported from tsutsugamishi triangle (2). The clinician has to make a decision at the earliest regarding diagnosis and cost effective treatment. The local prevalence and epidemiology of AES should be kept in mind.

Japanese Encephalitis is the Commonest Cause of Encephalitis in South East Asia

Japanese encephalitis virus was first isolated from human in Tokyo in 1935. JE virus activity was first detected in India in 1952 by Smithburn et al from Vellore (3). Till 1970 JE was restricted to south India in 1973. JE patients were reported from west Bengal, Bihar, Uttar Pradesh Assam and Andhra Pradesh (4-6). JE is mainly a disease of rural areas affecting the lower socio economic group. JE has scattered pattern of incidence average there are 1-1.5 patients per village. The ratio of clinical to subclinical cases ranges between 1:10 to 1:1000. JE mainly affects children but in east and north India all age groups are affected suggesting that the virus has been likely introduced in the respective area to relatively non immune population. Occurrence of JE cases has been reported in rainy season, floods, paddy cultivation and pig farming which provide environment for mosquito breeding and transmission of JE virus. Pigs are involved in maintaining and spread of JE virus through a pig, mosquitoes, pig cycle. JE virus is transmitted to the uninfected pigs by mosquito bite. The pigs suffer from a clinically in-apparent infection. As the mosquito's density increases there is spillover of the infection to human beings following a mosquito bite. Man is the dead end host because of transient and low level of viremia in cattle. The wading birds such as egret and herons are alternate amplifying host.

Pathogenesis

JEV is introduced into human body by mosquito's bite. The virus multiplies in the epithelial cell and rarely spread to the lymph nodes. The virus spread by primary viremia and further multiplies in the reticuloendothelial system and produces secondary viremia which deposits the virus in target organ such as brain, kidney and liver. Within 7 days of primary JEV infection a rapid IgM response occurs and by one-month IgM response decreases and IgG antibodies appear.

Clinical Presentation

The clinical picture of JE is derived into a prodromal period of 2-5 days, encephalitis stage of 1-3 weeks and convalescent phase of weeks to several months. The Patients present with fever and behavioral abnormality or altered sensorium which ranges from drowsiness to coma,
decerebration and decortication may also be present.

**Seizure**

In a study on 148 patients with AES Seizure were present in 42.6%; commonest being herpes simplex encephalitis (75%) followed by JE in 54%. The predictors of seizure were Glasgow coma scale (GCS) score cortical involvement on MRI. Seizure were related to 3-month outcome but not to mortality. CNS infection are commonest cause of status epilepticus (SE) in India and 30% patients with SE are due to viral encephalitis which refractory to anticonvulsants (7, 8).

**Anterior horn cell involvement**

Focal neurological signs appear as general condition of encephalitis patients improves and consciousness returns. The focal signs include hemiplegia, quadriplegia, cerebellar signs, lower motor neurons sign; cranial nerve palsy is in rare JE. Lower motor neurons sign manifesting with focal weakness, loss of tendon reflexes have been reported in acute stage of JE (9). In JE the muscle wasting is patchy and involves a few muscles of lower limbs or non-contiguous muscle or diffuse involvement of all 4 limbs. Concentric needle EMG after 3-4 weeks of encephalitis reveals profuse fibrillates in the affected muscle. The needle EMG after 3-month reveals, profound reduction or disappearance of fibrillation in the affected muscle. Motor and sensory nerve conduction are normal though motor action potential be reduced or un-recordable in some patients. The neurophysiological findings have been reported to be consistent with anterior horn cell involvement (9). There results were further confirmed in a larger study on 65 patients 23 of whom had anterior horn cell involvement but anterior horn cell involvement was not related to 3-month outcome (10).

**Movement disorder**

In the acute stage of JE, a wide variety of movement disorder such parkinsonian features dystonia chorea etc. have been reported (11, 12). In a study on 209 patients with encephalitis, 74 developed movement disorder 67.6% of these patients had JE, 51.2% had nonspecific encephalitis and 11.3% had dengue encephalitis (13). Three types of movement disorder have been reported in JE; transient form of Parkinsonism, dystonia and miscellaneous movement disorders. In a study on 50 patients 35 had movement disorder; 16 had Parkinsonism features and 19 had dystonia, in addition to Parkinsonian features. The prognosis of patients with only Parkinsonian features was better than those with additional dystonia (14). Dystonia in JE involves both the axial and limb muscle and commonly of fixed type resulting in retrocollis, opisthotonus mouth open and limb dystonia (Fig.1). Occasionally the dystonia in JE may be

![Fig 1. A 14 years old boy with JE showing severe axial and limb dystonia.](image)
very severe simulating status dystonicus. The dystonic spasms occur 10-30 times per day, each lasting for 10-30 minute with autonomic disturbance, swallowing, feeding and respiratory difficulty, fever and high serum CK level. These attacks are resistant to various to antidystonia therapies and regress over several months (15, 16). Dystonia is more common in children compared to adult and is associated with poor outcome compared to those without dystonia (17).

The movement disorder in JE are attributed to common involvement of thalamus basal ganglia and brainstem in MRI studies (18) and autopsy studies (19). The movement disorder appears as the patients recovers from coma. The basis of movement disorder in JE was associated with low CSF catecholamine levels. In the acute stage of encephalitis CSF noradrenalin, DOPEC, 5HT, HVA levels were significantly lower compared to controls. NE levels significantly correlated with dystonia and thalamic lesions (20).

Radiological Findings

CT scans findings in JE were first reported as low density areas in thalamus basal ganglia and substantia nigra (21). The changes in thalamus, insula, hippocampus and putamen are reported (22). We reported the diagnostic significance of radiological findings in the endemic area. The CT changes appeared within a week and if CT scan was normal the changes were evident on MRI as T2 hyper intensity in thalamus, basal ganglia and brainstem (Fig. 2) (23). On MRI study of JE patient, thalamus is involved in 94%, basal ganglia in 35% and midbrain 58% (24). Additional temporal lobe involvement in JE has been reported 17.7% patients (25).

The involvement of thalamus and its role in movement disorders: Dystonia and parkinsonian features are the commonest movement disorder in JE and occur in isolation in combination (51.3%). This is may be due to widespread MRI changes in thalamus basal ganglia and substantia nigra. Cortical activation disinhibits the striatum which is somatotopically organized and striatal m neurons and its collaterals to basal ganglia surround and inhibit the striatal neurons. Damage to the circuit involving thalamus basal ganglia, stratum and brain stem can result in different hyperkinetic or hypokinetic movement disorders (13). The parkinsonism features in JE may be due to the involvement of thalamus. The important role of thalamus in releasing basal ganglia inputs to

Fig.2 : Cranial MRI, T2 sequence axial section showing hyper intensity in thalamus and basal ganglia (A) and in midbrain (B)
motor cortex is well known. On SPECT study thalamus and frontal hypo perfusion was reported. These changes support the above mentioned mechanism of movement disorders in JE. The movement disorder irrespective of its severity regress over a period of time.

The basis of movement disorders was investigated in experimental rat model as well (26). The level of nor epinephrine, dopamine, 3,4-dihydroxyphenylacetic acid, homovalinic acid and serotonin were significantly decreased in thalamus midbrain, corpus stratum and frontal cortex. There was no significant recovery in catecholamine levels in behavioral and locomotor activities within 20 days of inoculation of JEV intracerebrally, however, histopathological changes revealed mild reduction in cell damage by 20dpi. These result supports the clinical studies and the CSF catecholamine levels in JE patients (26).

**Sequelae and Prognosis**

About 20-40% patients with JE die in the acute stage (27). 50% of surviving patients have serious, behavioral abnormality, focal weakness, seizure (20%) and a variety of movement disorder. The extent of MRI findings is not related to the outcome. The experimental studies on JE revealed impaired learning and memory function for 10-33 dpi. Improvement of memory learning was associated with reduction in expression of CHAT, HQNB CHR M2. These changes were followed by recovery after 30 dpi (28). These results are consistent with cognitive and behavioral impairment in JE and provide some information about its underlying mechanisms.

**Differential diagnosis**

The patients with JE needs to be differentiated for other causes of encephalitis but its differentiation from herpes simplex encephalitis is most important, dengue, malaria and scrub typhus are also important because of different therapeutic approaches. The differentiation between HSE and JE is crucial in the early stage. Behavioral abnormalities, seizures and status epilepticus were more common in HSE whereas focal reflex loss, and movement disorder were more common in JE. Behavioral abnormality and seizure are known features of HSE because of selective involvement of frontal, temporal limbic cortex (29-32) which is highly epileptogenic and has important role in modulating memory and behavior. Temporal lobe involvement in JE is less common and reported in 19% patients (25). Seizure in acute stage HSE have been reported in 40-60% (8, 33) and JE 7% to 69% (17, 34). JE is an meningoencephalomyelitis and anterior horn cell involvement occur in JE in autopsy studies (35, 36). A polio like illness in JE has been reported from Vietnam (37). Anterior horn cell less in JE may manifest with focal reflex less, weakness and wasting. MRI is invaluable in differentiating JE from HSE. Involvement of fronto- temporal cortex in HSE and of thalamus, brainstem and basal ganglia suggest in JE is highly suggestive.

There are number of other viral and non-viral condition which can which can simulate AES and have to be considered for rational and cost effective approach.

The diagnosis of AES varies according to the geographical region, and season because of differences in the prevalence of organism and their vectors. Geographically restricted encephalitis is mostly arthropod borne. The common cause of encephalitis in India are JE, dengue chikungunya, West Nile. However, malaria and scrub typhus are also common non viral infections in India. The patients with AES are generally evaluated with serum, CSF test, MRI, EEG. Those patients also receive empirical acyclovir and antibiotic therapy, taking care of most of the treatable etiologies.

A syndrome approach to AES has been suggested by us in which the patients are categorized into pure neurological or those with systemic manifestation such as rash,
thrombocytopenia, myalgia or raised serum creatinine kinase, liver or kidney dysfunction, lymphadenopathy etc. JE and HSE are prototype of pure neurological encephalitis group. In a study rash and myalgia separated these major groups of pure neurologic and systemic AES with high sensitivity and specificity. In pure neurological AES MRI helps in differentiating JE for HSE (38). In systemic AES group, dengue, scrub typhus, chickenguniya and malaria should be considered and treated with appropriate therapy: doxycycline for ST and artesonate for malaria and ceftriaxone for leptospirosis. In the systemic AES group MRI, PCR for HSE and JE IgM ELISA and acyclovir therapy may not be necessary. Using the above mentioned syndromic approach in diagnosis and treatment of AES can be substantially reduced (39).

Way Forward

The spectrum of encephalitis syndrome in dynamic, Vectors control and, environmental modification and vaccination would result in reduction of some causes of AES and their space would be occupied by other etiologies. Therefore, the spectrum of encephalitis may be changing. Autoimmune encephalitis triggered by infections may be recognized more commonly and pose therapeutic challenge. The syndromic approach in AES need to be consolidated and modified in different geographical regions as per local prevalence of pathogens for cost effective rational management of AES.

References


Trans-nasal Trans-sphenoidal Endoscopic Hypophysectomy

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ABSTRACT

Advances in optics, miniaturization, and endoscopic instrumentation have revolutionized surgery in the past decades. Current progress in the field of endoscopy promises to further this evolution: endoscopic telescopes and instruments have improved upon the optical and technical limitations of the microscope, and require an even less invasive approach to the sella. The minimally invasive endoscopic pituitary surgery is performed through the natural nasal pathway without any incisions and is performed via Trans-nasal Trans-sphenoidal approach. Pituitary surgery is traditionally within the realm of the neurosurgeon. However, since the introduction of the endoscopic transnasal transsphenoidal approach to the sella turcica for resection of pituitary adenoma, otolaryngologists have been active partners in the surgical management of these patients. Otolaryngologists have lent their expertise in nasal and sinus surgery, assisting the neurosurgeon with the operation. The otolaryngologist has the advantage of familiarity with the techniques and instruments used to gain exposure of the sella turcica by transnasal approach. Hence, the otolaryngologist provides the exposure, and the neurosurgeon resects the tumour. Such collaboration has resulted in decreased rates of complication and morbidity.

We hereby discuss our experience of treating 72 cases of pituitary tumour by endoscopic trans-nasal trans-sphenoidal approach. In our study, conducted from 2005 to 2016, the mean age of patients was 32.5 years (18-56 years), Male and female ratio was 1.3:1.0, MRI was done in all the cases, CT scan was done in 94.44% cases, 9.72% cases had Intra op./Post op. complications which were managed successfully. Subtotal resection could be done in 6.94% cases, recurrence was seen in 7.46% cases and lumbar drain was required in 4.17% cases. Average hospital stay was 4.4 days and average surgery time was 120 minutes. Close follow-up was maintained for an average period of 09 months. In our experience of 10 years, adopting the endoscope heightens the surgeons’ visualization of pituitary tumors, thus no external incision, no nasal packing and minimal stay with minimal complications. Endoscopic transsphenoidal approach is the less traumatic route to the sella turcica, avoiding brain retraction, and also permitting good visualization, with lower rates of morbidity and mortality.

Keywords: Endonasal; Transnasal, endoscopy; pituitary adenoma; surgical technique, trans-sphenoidal surgery.
Introduction

Significant advances in the recognition and management of pituitary adenomas have taken place over the last 2 decades. Highly sensitive hormonal assays and magnetic resonance imaging with gadolinium enhancement have led to earlier and more frequent diagnosis of pituitary adenomas. Since the early days of pituitary surgery, a variety of transnasal approaches have been used to gain access to the sella turcica. Each of these approaches requires crossing the sphenoid sinus, hence the transsphenoidal designation of these methods (1, 2). The surgical management of pituitary tumors has evolved over time from the transcranial to endonasal transsphenoidal approaches. Endoscopic pituitary surgery is an advancement over the microsurgical technique and has emerged as a better alternative to the microscopic transnasal transsphenoidal (TNTS) technique. An endoscopic transnasal sphenoidotomy approach without a septal dissection for resection of pituitary adenomas and other sellar lesions provided excellent exposure of the sella and adequate working space. The technique produces less postoperative pain and shortens hospital stay (3-6). The sphenoidotomy approach eliminates the problems of lip numbness, septal perforations, and oronasal fistulas. The endoscopic sphenoidotomy approach has become our preferred approach to sellar lesions (7). Endonasal endoscopy can be performed via either one or two nostrils (8-10).

Increasingly, the otolaryngologist is called on to provide exposure for the neurosurgeon performing transsphenoidal hypophysectomy. Multidisciplinary collaborations in managing complex pathologies of the skull base have evolved into a field of “neurorhinology” and this interaction with multiple specialities, notably otolaryngologists and neurosurgeons, has allowed procedures to be developed that offer significant advantages over treatment modalities (11). The team management of pituitary disorders is stressed. We reviewed our series of 72 patients undergoing transnasal hypophysectomy.

History

The evolution of pituitary surgery over the past century dates back to the work of Oscar Hirsch and Harvey Cushing in the early 1900s. Surgical approaches to pituitary adenomas have undergone significant adaptation since the first attempted transcranial and transsphenoidal decompression operations of the early 19th century.

In 1889 Horsley, using a transcranial approach is credited with performing the first operation for a pituitary tumor (12). In 1906 Schloffer reported the first removal of a pituitary tumor through an extracranial transsphenoidal approach (13). Hirsch later modified this approach in 1909. However, it was Cushing’s transseptal-transsphenoidal method introduced in 1910, which standardized this approach to pituitary tumors (14). The transseptal-transsphenoidal technique gained popularity throughout the early 1900s. Cushing himself reported on 247 pituitary tumors removed by this method between 1910 and 1929 (15). Inability to reach suprasellar tumor extension, poor illumination, CSF leakage, meningitis, and a high recurrence rate all led Cushing and his contemporaries to abandon the transseptal-transsphenoidal approach by the early 1930s in favor of the transcranial procedure (16).

It is Hardy however, who deserves much of credit for re-establishing the validity of the transsphenoidal approach, when in the 1960s he combined fluoroscopy and microsurgical techniques to further augment transsphenoidal pituitary tumor resection (15, 17). These new technologies provided the transseptal-transsphenoidal approach with significant advantages over the transcranial procedure. The improved visualization, allowed for more complete tumor removal, and reduced the incidence of complications. In the ensuing 40 years several large series have established the
Transsphenoidal approach as the procedure of choice for all but the most massive pituitary adenomas, demonstrating outcomes equivalent or better than those reported for the transcranial procedure with fewer complications (18, 19).

Microscopic transsphenoidal surgery has long been considered the “gold standard” in surgical treatment of pituitary tumors. The use of rigid endoscopes for sinus surgery provided the inspiration for their application to pituitary surgery (20). In 1992 Jankowski provided the first description of fully endoscopic transnasal-technique (12). At the beginning, the endoscope was mostly used as a microscope-assisted tool to explore the sella cavity for residual tumor. In 1997, the first clinical series of purely endoscopic pituitary surgery was reported by Jho and Carrau. Jho has published relatively large series describing his experience with 44 pituitary adenomas and 6 other parasellar lesions (13). Reports have suggested that in addition to providing more complete tumor removal, the endoscopic technique may also result in a lower incidence of complications related to blind dissection (21-24). Since then, many pituitary surgeons gradually shifted towards an endoscopic endonasal approach for pituitary adenomas and other parasellar tumors. The recent development of endoscopic instrumentations and techniques has contributed in enhancing the efficacy and safety of the endoscopic approach and has further promoted the shift.

Over the last two decades, endoscopic endonasal surgery has gradually gained favor as a primary approach for sellar and parasellar lesions, primarily due to the wide panoramic, up-close visualization offered by the endoscope. Angled endoscopes allow for complete resection of high-grade (invasive) tumors, visualizing parasellar and suprasellar tumor extension, and allowing for rapid decompression of the optic chiasm. Often, the full extent of extrasellar tumor growth is not visible with the direct line of site of the operating microscope (25).

Patients with massive suprasellar tumor extension are recommended to undergo a transcranial approach.

**Surgical Procedure**

The operation takes place with the patient supine The head of the bed is elevated and the patient's neck is slightly extended and rotated toward the nostril to be used for the procedure. Depending on the pre-operative assessment of the patients nasal passageway a 4 mm endoscope is used. The video monitor is positioned behind the patient's shoulder directly opposite the surgeon's line of vision. The 0° endoscope is used to guide the intranasal dissection and initial tumor resection. Initially sphenoid ostia is identified and sphenoidotomy is done (infero-medially), sella turcica is identified, mucosa over sella is removed and sella bone is removed (using sickle knife/perioisteal elevator/drill). Exposed duramater is cauterized and cut in a cruciate manner. After taking tissue for histopathology, tumor resection is carried out using a suction device and ring curettes of varying diameter and orientation (26).

**Surgical Steps**

The surgical technique includes four stages, namely, the nasal stage, the sphenoidal stage, the sellar stage and the reconstruction stage. Recognition of important landmarks during each of these stages is the key to a safe exposure (Figs. 1- a,b,c,d).

All operations are performed via a single/double nostril approach. Once tumor resection is complete or residual tumor is outside the field of view, the 0° endoscope is withdrawn and a 30° endoscope is inserted. The angled lens of this endoscope provides excellent exposure of the suprasellar and parasellar regions. Rotating the 30° endoscope clockwise and counterclockwise provides visualization of suprasellar and parasellar tumor extension, including invasion into the cavernous sinus if
Patient Positioning

<table>
<thead>
<tr>
<th>A. Nasal stage</th>
<th>Patient supine, head of the bed is elevated and the patient’s neck is slightly extended and rotated toward the nostril to be used for the procedure.</th>
</tr>
</thead>
<tbody>
<tr>
<td>B. Sphenoid stage</td>
<td>Nasal Ethmoid / Turbinate stage</td>
</tr>
<tr>
<td>C. Sellar stage</td>
<td></td>
</tr>
<tr>
<td>D. Reconstruction</td>
<td></td>
</tr>
</tbody>
</table>

Fig. 1: Four phases / steps of surgical Trans-nasal Trans-sphenoidal Endoscopic Hypophysectomy

a. Both sides sphenoidal ostia identified (widened), posterior nasal septum (vomer) removed,
b. Sella turcica bone removed, duramater exposed,
c. Duramater incised by cruciate incision,
d. Pituitary Tumour curreted with ring curette and cavity explored.
Any residual tumor is resected, eliminating areas of potential tumor recurrence. Once tumor resection is complete, the area is irrigated and hemostasis is obtained. An abdominal fat graft is harvested and used to reconstruct the sellar defect, which is then sealed using surgicel and abgel. Nasal packing is done with merocel which is removed after 48 h (24).

### Complications and their Avoidance

These can be divided into two major categories: (1) Nonendocrinal; and, (2) endocrinal complications- (27, 28) (Table 1).

#### Table 1: Complications and their avoidance (27)

<table>
<thead>
<tr>
<th>Complications</th>
<th>Causes</th>
<th>Avoidance</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Nonendocrine</strong></td>
<td></td>
<td></td>
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<tr>
<td>A. Nasal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anosmia/hyposmia</td>
<td>Excessive mucosa coagulation</td>
<td>Avoid mucosal coagulation in upper nasal septum of at least 1 cm</td>
</tr>
<tr>
<td>Saddle nose deformity</td>
<td>Extended Posterior septectomy</td>
<td>Avoid excessive removal of cartilaginous nasal septum</td>
</tr>
<tr>
<td>Epistaxis (early or delayed)</td>
<td>Bleeding from posterior septal artery (branch of sphenopalatine artery)</td>
<td>Bipolar coagulation of posterior septal artery located superolateral to choana, at inferolateral corner of sphenoethmoidal recess, at medial posterior corner of inferior margin of MT</td>
</tr>
<tr>
<td>Synechiae/nasal crusting</td>
<td>Raw area/mucosal damage</td>
<td>Keep mucosal damage minimal, Leave minimal raw area, Remove all foreign material</td>
</tr>
<tr>
<td>B. Sphenoidal complications</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sinusitis/mucocele</td>
<td>Improper removal of mucosa</td>
<td>If needed, pack the whole sphenoid, with removal of the entire mucosa</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Medialize middle turbinate in the end to avoid sinusitis/mucocele</td>
</tr>
<tr>
<td>C. Carotid injury</td>
<td>Cavernous segment is most vulnerable</td>
<td>Study preoperative CT, MRI for kissing carotids, anomalous position, and bone dehiscence (20%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Keep always oriented by checking that buttons of the camera are facing the screen</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Use navigation</td>
</tr>
<tr>
<td>D. Cranial</td>
<td>Inadvertent entry into Anterior Clinoid Process</td>
<td>Do not enlarge ostium superiory</td>
</tr>
<tr>
<td>CSF leak/meningitis/pneumocephalus</td>
<td>Blind dissection</td>
<td>No blind dissection to prevent arachnoidal tear</td>
</tr>
<tr>
<td></td>
<td>Pulling tumor without mobilization</td>
<td>Tumor should be mobilized first and then sucked in suction</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Use &quot;flashlight effect&quot; to visualize and differentiate arachnoid from diaphragm</td>
</tr>
<tr>
<td></td>
<td></td>
<td>If cerebrospinal fluid leak occurs. Immediately seal the rent and reconstruct sellar floor</td>
</tr>
<tr>
<td>E. Postoperative apoplexy/bleed/swelling/ in residual tumor</td>
<td>Incomplete tumor removal</td>
<td>Always remove maximum tumor</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Use extended approach with removal of tuberculum sella and mOCR (cause of constriction) in large Supra sellar extension Use image guidance, angled scope and instruments</td>
</tr>
<tr>
<td>F. Sub Arachnoid Haemorrhage and vasospasm</td>
<td>Fixing the scope Arachnoidal tear</td>
<td>use four-hand technique and flashlight effect and avoid arachnoidal tear</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Do not fix the scope</td>
</tr>
<tr>
<td></td>
<td></td>
<td>If occurs, seal it immediately with glue and prevent further opening</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Use cotton patty to cover the arachnoidal defect to prevent blood going into the subarachnoid space</td>
</tr>
<tr>
<td>G. Perforator injury</td>
<td>Blind dissection</td>
<td>Remove tumor under vision, using &quot;flashlight effect&quot;</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No infra-arachnoidal dissection</td>
</tr>
<tr>
<td>H. Decreased vision</td>
<td></td>
<td>Avoid overzealous sellar packing</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Maximal tumor resection to avoid postoperative apoplexy</td>
</tr>
<tr>
<td>I. Hydrocephalus</td>
<td></td>
<td>Remove maximal tumor/avoid arachnoidal tear</td>
</tr>
<tr>
<td><strong>Endocrine</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Worsening/new endocrine dysfunction</td>
<td>Damage to normal pituitary</td>
<td>Always predict position of normal pituitary in preoperative MRI</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Intraoperatively- it is pinkish, firm, nonsuckable, with presence of vasculature on surface</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Thinned out residual normal pituitary tissue appears as an apron plastered to the undersurface of diaphragm</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Normal pituitary should be preserved (even 10% is enough)</td>
</tr>
</tbody>
</table>
Materials and Methods

Surgery for pituitary tumours was performed by rhinosurgical route by combined procedure by otorhinolaryngologist and neurosurgeons. A retrospective review of case records of patients who had endoscopic endonasal transsphenoidal approach for pituitary tumours under general anaesthesia from 2005 to 2016 was performed. A total of 73 transphenoidal surgeries were performed during this study period. Only 72 case records with adequate information were available for review, which were for primary 68 (94.4%) or recurrent pituitary adenomas (05.6%).

Observations

The mean age of patients was 32.5 years (18-56 years). There were 41 females (56.94%) and 31 males (43.06%). Female and male ratio was 1.3:1.0. In our series, the peak age was fifth decade (50-60 years) accounting for 28 (38.9%) patients. Endocrinal status was assessed and medical fitness for surgery was ascertained. Out of total 72 pituitary adenomas, 58 (80.5%) were hormonally active (functional), while 14 (19.5%) were non-functioning. 68 (94.4%) were macroadenoma (> 10 mm), and 04 (5.6%) were microadenoma (< 10 mm). 38 patients (55.88%) out of 68 macro-adenoma had suprasellar extensions.

Other than hormonal symptoms the most common presenting complaints included visual symptoms—changes in visual acuity or visual field deficits (61) (84.72%) headache (56) (77.77%) menstrual cycle disturbance or infertility /impotence (18) (25%), and acromegalic features (16) (22.22%).

Preoperative magnetic resonance (MR) imaging were obtained in all the patients, and CT scans were obtained in 68 (94.44%) patients. The exquisite definition of the bony boundaries of the sinus, provided by thin-sliced axial and coronal computerized tomography (CT) scans, was essential to assess the symmetry and aeration of the sphenoid sinus and to decipher the relationship of the sphenoid sinus septum to the sella turcica floor and carotid canals. The operation was performed under general anesthesia has been induced in the patient via orotracheal intubation. Intranasal packing was occasionally used and removed on the second post-operative day. Only 03 patients (4.17%) had lumbar drain inserted prior to commencement of the surgery and all these were macroadenomas.

Subtotal resection could be done in 5 (6.94%) cases with residual tumor in the cavernous sinus. Recurrence was seen in 5/67 (7.46%) cases, Five of the patients demonstrating recurrent tumor had a mass ranging from 5 to 8 mm on an MRI scan performed postoperatively, two of them underwent revision surgery and 3 of them having recurrence were referred for Gamma knife surgery. 07 cases (9.72%) had Intra op./Post op. complications which were managed successfully. The common complications encountered were Nasal synechae- 03 (4.16%), diabetes insipidus- 1 (1.39 %), cerebrospinal fluid leak-1(1.39%), epistaxis- 1 (1.39%)- postoperative sphenopalatine bleed, septal perforation-1 (1.39%). The CSF leaks were controlled by vascularized mucosal flaps which hastens the healing process. Hadad nasoseptal flap, supplied by the posterior nasoseptal arteries which are branches of the posterior nasal artery was used in 01 case. There was no mortality in our series.

Average hospital stay was 4.4 days and average surgery time was 120 minutes. Close follow-up was maintained for an average period of 09 months The most common indications for longer hospitalization included temporary diabetes insipidus and prior co-morbid conditions which required extended monitoring or rehabilitation. Patient outcomes were determined from intra-operative assessment of tumor resection, postoperative hormonal levels and MR imaging results. MR imaging studies were performed for all patients during the early
postoperative period, to be repeated after 6–12 months and then annually for the rest of their follow-up period. Remission, being defined as no hormonal or radiological evidence of recurrence within the time-frame of the follow-up. Remission was demonstrated in 62/72 (86.1%) of adenomas.

**Discussion**

Microsurgical transsphenoidal surgery for pituitary adenoma has been the standard treatment for decades in the neurosurgical community (2, 8). Jankowski et al. first reported the successful endonasal endoscopic resection of pituitary adenomas in three patients. They removed the middle turbinate to gain access to the sphenoid sinus. They performed the operation via one nostril in two patients and via both nostrils in another (12). Sethi and Pillay reported approximately 40 patients in whom they had performed endoscopic pituitary surgery via either the transnasal transseptal or ethmoidectomy approach with a sphenoid retractor (14). The use of thin-sliced axial and coronal CT scans is essential to avoid unexpected findings from anatomical variations in the sphenoid sinus. Magnetic resonance imaging alone will not provide the necessary detail of bone anatomy of the sphenoid sinus.

In general, pituitary adenomas are diagnosed more frequently in women than in men probably because of the association of these tumours with menstrual irregularities (11) which correlates with our study. The incidence of pituitary adenoma increases with age, peaking between the third and sixth decades (11). In our series also, the peak age was fifth decade (50-60 years) accounting for 28 (38.9%) patients.

Pituitary adenoma can be divided into functioning and non-functioning tumours, or
according to size namely microadenomas or macroadenomas. Functioning pituitary adenomas can be clinically classified by means of the hormone they secrete. These tumours become symptomatic because they secrete hormones such as growth hormone, adrenocorticotropic hormone (ACTH) and prolactin.

The incidence of residual tumour is higher in pituitary macroadenoma. This is probably due to size and extension of tumour to surrounding structures namely suprasellar extension to optic chiasm and lateral extension to engulf the internal carotid artery. Twenty eight percent of pituitary macroadenomas can extend into the cavernous sinus as reported in the literature (29). Complete removal in macroadenoma may be difficult without adequate decompression. In our series, Subtotal resection could be done in 5 (6.94%) cases with residual tumor in the cavernous sinus. Recurrence was seen in 5/67 (7.46%) cases.

Complications of endoscopic surgery of the paranasal sinuses can be classified according to the severity as minor or major and according to the time of appearance as immediate or delayed. Minor complications occur in between 2 and 21% (30) of cases which include synechia, crusts, minor bleeding, nasal septum perforation, headache, facial pain, alteration of dental sensitivity, edema, local infection, periorbital ecchymosis, palpebral edema, subcutaneous emphysema, stenosis of sinus ostia, hyposmia, epiphora, exacerbation of bronchial asthma, and postoperative sinusitis, this goes in coherence with our study (9.72%). The principal major complications anticipated are vascular injury and orbital and intracranial complications which vary from 1 to 3% (Table 2). The most frequent immediate complications are CSF leak, intraoperative bleeding, orbital hematoma and injury to brain (27, 28). Delayed complications include progressive loss of vision (24) or smell, meningitis, bleeding, synechia, and infection.

**Future Advances**

Over the past several years, endoscopic technology, instrumentation, and relevant anatomical mastery have promoted many innovative methods and approaches to the extrasellar regions. The new developed instrumentations include high definition 3D endoscopic system, (31) endoscopic augmented reality navigation system, (32) ultrasonography-assisted endoscope, (33) the indocyanine green fluorescence endoscope, (34) and use of high-field intraoperative MRI, (35) et al. These are reported to increase the safety and reduce the risk of the endoscopic approach (Table 3). Recently, an experimental feasibility study on

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**Table 2 : Contraindications-trans-nasal trans-sphenoidal endoscopic hypophysectomy**

- Poor general condition of patient
- Conchal type of sphenoid pneumatization
- Sphenoid sinus infected
- Highly vascular lesions
- Dural-based lesions with a high risk for intraoperative and postoperative cerebrospinal fluid leak
- Extensive suprasellar extension and carotid artery anatomy, wherein the arteries project into the sphenoid sinus and limit safe access
- Multi Septate Sphenoid
robotic endonasal telesurgery was reported (36). 4K (and 8K) ultra-high definition endoscopes are likely to be introduced to this field in the near future (14).

The extended endoscopic surgery to the midline ventral skull base have been extensively developed and refined for removal of parasellar tumors including suprasellar adenomas, craniopharyngiomas, chordomas, chondrosarcomas, meningiomas, et al. The advantages and benefits of the endoscope can be more appreciated in the extended surgery for these parasellar tumors than the pituitary surgery (37).

**Conclusion**

Currently, the Transnasal Transsphenoidal (TNTS) hypophysectomy approach represents the standard approach by which the vast majority of pituitary adenomas are surgically resected. Endoscopic pituitary surgery is useful in all micro- and macro-pituitary adenomas including those with suprasellar and cavernous sinus extension. The endoscope provides a panoramic close-up, a multi-angled view with excellent illumination and magnification, permitting complete excision of the tumor with preservation of normal pituitary and a reduced incidence of complications. The results of this fully endoscopic transnasal series are quite encouraging. We echo the statements of Jho regarding the challenges to successful outcomes: “Certainly, a learning curve exists for a surgeon who is not familiar with the endoscope. A surgeon inexperienced with this technique may become frustrated if the two instruments consistently strike each other in the small operating space (38). Traditionally pituitary tumours have been removed by neurosurgeons through the cranial approach but the advent of nasal endoscopes has opened new avenues for ENT surgeons to treat such patients (39). We believe that the inherent advantages of endoscopic visualization, along with continued refinement of the endoscopic technique and instruments will allow this method to become the future gold standard surgical approach to pituitary adenomas.

<table>
<thead>
<tr>
<th><strong>Table 3: Advantages and disadvantages of trans-nasal trans-sphenoidal endoscopic hypophysectomy</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Advantages</strong></td>
</tr>
<tr>
<td>Better illumination and superior visualization as the light source is close to the target</td>
</tr>
<tr>
<td>Wide angle view and visualization of the opticocarotid recess (OCRs) as well as carotid and optic protuberances</td>
</tr>
<tr>
<td>Angled endoscopes expand the range of visualization including visualization of corners and hidden angles permitting complete removal of the tumor</td>
</tr>
<tr>
<td>A high image resolution permitting more accurate differentiation between the diaphragm sellae and the arachnoid, and between the normal and neoplastic tissue enabling preservation of normal pituitary</td>
</tr>
<tr>
<td>Avoidance of nasal speculum and packing causes less postoperative discomfort and an early return to work</td>
</tr>
</tbody>
</table>
Acknowledgement

The major part of the work was done at my previous institute- Himalayan Institute of Medical Sciences, Dehradun

Conflicts of Interest Disclosure

There are no conflicts of interest, no commercial relationships, no support from pharmaceutical or other companies. The author has no personal or institutional financial interest in drugs, materials, or devices described in the present paper.

References


Shoulder Periarthritis and its Imaging Features in Patients with Type 1 Diabetes Mellitus

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ABSTRACT

Aim: There is limited information on periarthritis/adhesive capsulitis of the shoulder (ACS) in patients with type-1-diabetes mellitus (T1D). We assessed the prevalence and characteristics of ACS in patients with type-1-diabetes mellitus.

Methods: Consecutive 267 patients attending 'Diabetes of Young Clinic' were screened for ACS. Those with clinical features of ACS were further assessed by 'shoulder pain and disability index' (SPADI), radiograph and MRI of the shoulder. The average glycemic status (HbA1c) during preceding 2 years was assessed in patients with and without ACS. Controls were age and sex matched healthy subjects (1:1 ratio).

Results: Sixteen of 267 patients (6.0%) with type-1-diabetes had clinical features of ACS, unlike none of the healthy controls (P < 0.001). Internal and external rotation of the shoulders was the most frequently restricted movements in ACS. Thickened coracohumeral ligament and axillary pouch obliteration was characteristic MRI feature, present in 80.0% in 73.3% cases, respectively. Though 14/16 type-1-diabetes patients with ACS were symptomatic, they never reported these complaints in diabetic clinic with the treating physicians. On regression analysis (odds ratio; 95% CI), duration of diabetes (1.1; 1.03-1.17, P < 0.01), retinopathy (3.6; 1.05-12.52, P = 0.04), and limited joint mobility (6.4; 1.88-21.95, P < 0.01) were independent predictors for presence of ACS in type-1-diabetes. The mean HbA1c and lipid levels were comparable in patients with or without ACS.

Conclusions: Six percent of patients with type-1-diabetes had ACS, which can be detected on clinical screening and confirmed by imaging to help initiate early treatment.

Keywords: Type1 Diabetes, complications.

Correspondence: Dr. Ravinder Goswami, MD, DM (Endocrinology), Department of Endocrinology and Metabolism, All India Institute of Medical Sciences, New Delhi-110029. Email: gosravinder@hotmail.com.
However, to date there is no systematic study describing the clinical aspects, prevalence and imaging features of ACS in patients with Type 1-diabetes. Here we describe the prevalence of ACS, clinical features, related disability and the magnetic resonance imaging (MRI) characteristics of ACS in a large cohort of 267 patients with type 1 diabetes.

**Material and Methods**

Patients with type-1-diabetes were recruited from the 'Diabetes of Young Clinic' at 'All India Institute of Medical Sciences', New Delhi. Patients with onset of diabetes < 30 years of age are registered and followed-up in this clinic since 1990. All the patients attending the clinic during a six-month period were examined for the presence of adhesive capsulitis of shoulder by a clinician and an occupational therapist (authors AN and HB). Those with duration of diabetes less than two years, pregnancy, history of trauma or any other disease affecting the shoulder region were excluded. The details of duration, onset of diabetes, associated thyroid dysfunction, presence of retinopathy (as confirmed by ophthalmologist) and GAD65 autoantibody positivity were noted from the records of the patients maintained in the clinic. Peripheral neuropathy was assessed using symptoms and signs scores as suggested by Meijer et al (7). Estimated glomerular filtration rate (eGFR) was calculated as suggested by Cockcroft and Gault (8). Glycemic control was assessed by average of the last four HbA1c values of the patients. A fresh blood sample was also drawn for their current HbA1c.

**Diagnosis of Adhesive Capsulitis**

ACS was diagnosed based on the criteria suggested by the 'American shoulder and elbow association' (9-11). The essential criteria were restriction of active and passive movements of the shoulder and absence of other intrinsic shoulder disorders. Restriction of shoulder movements was assessed by Apley's scratch physical test (9). In this test, patients were asked to reach behind the head and touch the superior aspect of the opposite scapula with the hand to assess their abduction and external rotation. Internal rotation and adduction of the shoulder were tested by asking the patient to reach behind the back and touch the inferior aspect of the opposite scapula. Patients with positive Apley's test were examined by an orthopedic expert (authors HLN). The range of shoulder joint motion in active condition was quantified during flexion, extension, abduction external and internal rotation using a universal goniometer (Baseline, New York). A restriction of movement of more than 25% in any of these was considered significant. To assess association between ACS and limited joint mobility (LJM) of hand, patients were also examined for the presence of 'prayer sign' (12).

**Shoulder Pain and Disability Index (SPADI)**

Pain and functional loss related to ACS were assessed by SPADI as per the recommendation of 'American Physical Therapy Association' (13-15). SPADI is a self-administered questionnaire with five questions on severity of pain and eight questions on disability during activities of daily living. Responses to the questions were graded on visual analog scale where '0' indicated no pain/disability and 10 being the maximum. The highest possible scores for pain and disability were 50 and 80, respectively.

**Imaging for the Shoulder Joint**

Patients with restricted movements were subjected to radiography and non-contrast MRI of the affected shoulder joint. If restriction was present in both the shoulder joints, the more severely affected one was imaged. The MR scans were evaluated by two radiologists (authors, RS and DK) and findings were recorded by consensus.

Controls were healthy nursing and medical students of the Institute and acquaintances of the patients. They were age and
sex matched (± two years) in 1:1 ratio with the patients' cohort. The study was approved by the ethics committee of the All India Institute of Medical Sciences, New Delhi. Written informed consent was obtained from all the subjects undergoing radiographs and MRI studies. The work was carried out with the support of financial grant from Indian council of Medical Research (#5/4/5-5/Diab.-16-NCD-II).

**Statistical Analysis**

Data are shown as mean ± SD with frequencies in percentage. The clinical and biochemical characteristics of patients with and without ACS were compared by parametric and nonparametric tests as appropriate. The differences in the frequency of ACS between patients and controls were compared using Fisher's exact test. A two tailed P value < 0.05 was considered significant.

**Results**

Figure 1 shows the flow of patients in the study. A total of 300 subjects with type-1-diabetes attended the clinic during the study period. Controls included 267 subjects during the same period. Two hundred ninety of type-1-diabetes could be contacted to participate in the study. Twenty three of 290 subjects with type-1-diabetes were excluded for various reasons (significant injury around shoulder in the past, n = 9; duration of diabetes < 2 yrs, n = 9; and n = one patient each with severe kyphoscoliosis, multiple sclerosis, furuncle over shoulder, past history of joint tuberculosis and age of onset of diabetes > 30 yrs). Final results are reported for a total of 267 patients (M:F 134:133). Table 1 shows the clinical characteristics and biochemical features of the patients. Their mean age, body mass index and duration of diabetes were 26.6 ± 10.7 years, 20.4 ± 3.7 kg/m² and 13.0 ± 8.4 years respectively. Thyroid dysfunctions were present in 38 (14.2%) of them (hypothyroidism, n = 35, and Graves' disease, n = 3). However, all these patients were euthyroid on appropriate treatment. History of diabetic ketoacidosis was present in 189 patients. GAD65 antibody was positive in 103 of the 181 type-1-diabetes patients in whom test results were available. Limited joint mobility of hand joints was present in 30 (11.2%) of type-1-diabetes patients.

The M:F ratio and the mean age of the healthy controls (134:133 and 26.9 ± 10.8 years) was comparable to that of type-1-diabetes patients (P = 0.96 and 0.72, respectively).

**Prevalence of Adhesive Capsulitis**

Sixteen of the 267 patients with type-1-diabetes (6.0 %) had clinical features of ACS. In contrast, none of the controls showed restriction of any movement of the shoulder joints (P < 0.001). Restriction of internal (n = 13) and external rotation (n = 8) were the most common abnormalities and all of them demonstrated restriction of either one or both of these movements. In addition, extension was restricted in seven of them and flexion and abduction movements were restricted in three each. The range of shoulder joint movements on goniometry was reduced by 40 ± 11.4% for internal rotation, 31 ± 17.8% for external rotation, 19 ± 19.4% for abduction, 23 ± 11.6% for extension and 17.2 ± 16.2% for flexion. The median SPADI scores for pain and disability were 6 (range 0-29) and 14 (range 0-49), respectively.

**Clinical Characteristics of Patients with and without Adhesive Capsulitis of Shoulder**

Table 1 shows the clinical and biochemical characteristics of patients with and without ACS. The mean age (37.0 ± 11.6 years) and duration of diabetes (24.1 ± 11.6 years) of patients with ACS were significantly different from those with no ACS (26.3 ± 10.36 years and 12.5 ± 7.62 years, P < 0.01 and P < 0.05, respectively). The prevalence of retinopathy and neuropathy was significantly higher in patients with adhesive capsulitis compared to those with no such features (Table 1). Similarly, LJM was present in
Patients attending diabetic clinic of young during study period \( (n = 300) \)

Could not be contacted \( (n = 10) \)

Patients contactable \( (n = 290) \)

Excluded \( (n = 23) \)
- History of shoulder injury \( (n = 9) \)
- Duration of DM < 2 years \( (n = 9) \)
- Kyphoscoliosis \( (n = 1) \)
- Multiple sclerosis \( (n = 1) \)
- Age of onset of DM > 30 yrs \( (n = 1) \)
- Furuncle over shoulder \( (n = 1) \)
- Shoulder joint TB \( (n = 1) \)

Clinical assessment for ACS \( (n = 267) \)

No ACS \( (n = 251) \)

ACS present \( (n = 251) \)

Pregnant woman excluded for imaging \( (n = 1) \)

X ray and MRI of shoulder \( (n = 15) \)

Radiologic features of ACS \( (n = 14) \)

Normal imaging \( (n = 1) \)

Fig. 1: Flow of patients in the study
Table 1: Characteristics of type 1 diabetes patients with and without adhesive capsulitis of shoulder

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Adhesive capsulitis</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Present (n=16)</td>
<td>Absent (n=251)</td>
</tr>
<tr>
<td>Sex (M:F)</td>
<td>7:9</td>
<td>127:124</td>
</tr>
<tr>
<td>Age (years)</td>
<td>37.0 ± 11.6</td>
<td>26.0 ± 10.4</td>
</tr>
<tr>
<td>Duration of diabetes (years)</td>
<td>24.1 ± 11.6</td>
<td>12.3 ± 7.6</td>
</tr>
<tr>
<td>Body mass index (Kg/m²)</td>
<td>21.2 ± 3.8</td>
<td>20.3 ± 3.8</td>
</tr>
<tr>
<td>Hypothyroidism (%)</td>
<td>12.5%</td>
<td>13.1%</td>
</tr>
<tr>
<td>Current HbA1c (%)</td>
<td>9.0 ± 2.5</td>
<td>9.2 ± 2.2</td>
</tr>
<tr>
<td>Average pooled HbA1c (%)</td>
<td>9.0 ± 2.0</td>
<td>9.2 ± 2.7</td>
</tr>
<tr>
<td>Total cholesterol (mg/dL)</td>
<td>169 ± 28.8</td>
<td>165 ± 34.3</td>
</tr>
<tr>
<td>Serum triglycerides (mg/dL)</td>
<td>107 ± 48</td>
<td>100.4 ± 52.0</td>
</tr>
<tr>
<td>Serum LDL (mg/dL)</td>
<td>90 ± 30</td>
<td>92.5 ± 28.3</td>
</tr>
<tr>
<td>Serum HDL (mg/dL)</td>
<td>54.5 ± 13.5</td>
<td>54.0 ± 17.6</td>
</tr>
<tr>
<td>Proteinuria &gt; 150 mg/day (n)</td>
<td>1 (6.2%)</td>
<td>20 (8.3%)</td>
</tr>
<tr>
<td>Serum creatinine (mg/dL)</td>
<td>0.8 ± 0.3</td>
<td>0.8 ± 1.1</td>
</tr>
<tr>
<td>eGFR &lt; 60 ml/minute</td>
<td>2 (12.5%)</td>
<td>18 (7.1%)</td>
</tr>
<tr>
<td>Diabetic retinopathy (n)</td>
<td>9 (56.2%)</td>
<td>32 (12.7%)</td>
</tr>
<tr>
<td>Neuropathy (n)</td>
<td>9 (56.2%)</td>
<td>31 (12.4%)</td>
</tr>
<tr>
<td>Limited joint mobility (%)</td>
<td>43.7%</td>
<td>9.6%</td>
</tr>
</tbody>
</table>

Magnetic resonance imaging (MRI) features of the shoulder joint were assessed in 15 of the 16 patients with ACS. One patient was pregnant and was excluded from imaging. Table 2 shows the frequencies of salient features of ACS on MRI. Thickening of the coraco-humeral ligament was the most frequent abnormality (n=12, 80%), followed by axillary pouch obliteration (n=11, 73.3%) (Fig. 2). Other features included thickening of capsule over axillary pouch (n=8, 53.3%), sub-coracoid fat pad obliteration (n=8, 53.3%) and supraspinatus tendinitis (n=4, 26.6%). On plain radiograph, four of 15 (26.6%) also had sclerosis of the greater tuberosity of humerus.

Discussion

In the present study, patients with type 1 diabetes mellitus...
diabetes were actively screened for the presence of ACS of shoulder, its significance on their daily activities and the imaging characteristics were assessed. Further, association of ACS with glycemic control and other chronic complications of diabetes were sought. The study revealed a 6.0% prevalence of ACS among patients with type-1-diabetes. The observed prevalence was similar to that of Arkkila et al., who also observed 10.3% prevalence of ACS in type-1-diabetes. The mild difference in prevalence rate of ACS in type-1-diabetes observed by Arkkila et al., could be due to the higher age and duration of diabetes of their cohort (higher by five years each). Interestingly, the longer duration of diabetes with ACS was also forthcoming in the present study. In the present study, on an average, patients with ACS were a decade older than those without ACS and also had longer duration of diabetes by 12 years compared to those with no feature of ACS.

The patients with ACS had longer duration of diabetes and prevalence of diabetic complications of neuropathy and retinopathy (56.2% for each) as compared to those with no ACS. With each year increase in duration of diabetes, the prevalence of ACS increased by 11%. The odds of presence of ACS in type-1-diabetes patients were 6.4 times higher if they had LJM. The occurrence of ACS with increasing duration of diabetes and microvascular complications justifies its reference as another form of chronic complication among patients with type-1-diabetes. Despite association of ACS with chronic complications, we did not observe a significant difference in the HbA1c levels between patients with and without ACS. There has been no systemic study on the association of long term glycemic control with ACS in patients with type-1-diabetes. However, patients with type 2 diabetes show variable association of glycemic status with ACS (16-19). Prospective

<table>
<thead>
<tr>
<th>Combination</th>
<th>Coracohumeral ligament thickening</th>
<th>Axillary pouch obliteration</th>
<th>Thickening of capsule over axillary pouch</th>
<th>Subcoracoid fat pad obliteration</th>
<th>Supraspinatus tendinitis</th>
<th>Frequency of combination</th>
</tr>
</thead>
<tbody>
<tr>
<td>Combination 1</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>1</td>
</tr>
<tr>
<td>Combination 2</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
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+ve = present, -ve - = absent
Fig. 2: T1 weighted MR images (A, B) in sagittal oblique plane showing normal appearance of coracohumeral ligament (arrow in image A) and abnormally thickened coracohumeral ligament with surrounding fat stranding (arrow in image B). T2 weighted fat suppressed images (C, D) in coronal oblique plane showing normal axillary pouch (black arrow in image C) and thickening of capsule with obliteration of axillary pouch (black arrow in image D). There is supraspinatus tendinitis with associated marrow edema also seen (white arrow in image D).

studies would help understand the interplay between long term glycemic control and ACS.

The restricted shoulder movements were functionally relevant as revealed by mild to moderate impairment in SPADI score for pain and disability. Shoulder pain and disability could lead to difficulty in concentrating, working and interference in their daily activities like insulin injection and physical exercise involving upper limb. Interestingly, despite evidence of ACS and its functional impact, 14 of the 16 patients with ACS were newly detected in the study. These patients were referred for expert care. The reasons for inability of the patients to seek medical advice by a majority of the patients are not known. However, several factors could be contributory including lack of awareness of this condition or their pre-occupation with a host of other problems related to diabetes. Notwithstanding these, the current study shows that ACS could be a significant problem in patients with type-1-diabetes akin to type 2 diabetes and needs to be assessed during routine
follow-up. The present study also showed that coraco-humeral ligament thickening and/or axillary pouch obliteration in more than 90% of them on MRI could provide objectivity to the clinical diagnosis of ACS.

Conflict of Interest

There are no conflicts of interest relevant to this article among the authors.

References


Favorable Pregnancy Outcome in a Patient with Uncorrected Uni-ventricular Heart - A Case Report and Review of Literature

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ABSTRACT

Univentricular heart or a heart with a double inlet ventricle is a rare congenital cardiac anomaly that poses a great challenge for the clinicians owing to increased maternal and fetal complications. It may even lead to maternal mortality. We here describe a case that was managed efficiently and successfully in a low resource setting.

Keywords: Univentricular heart, pulmonary stenosis, aortic stenosis, low resource setting.

Introduction

Of the seven per 1000 live infants born with congenital heart disease, over 85% now survive into adult life (1). Single ventricle represents a rare abnormality found in 3.2% of patients with congenital heart disease (CHD), often discovered during childhood (2). Pregnancy with this rare complex congenital heart disease poses a great challenge to the obstetrician. We, here report a case of successful outcome in a pregnancy with double inlet ventricle and pulmonary stenosis and discuss the literature review.

Case Report

A 23 years old primi-gravida at 32 weeks gestation with complex congenital heart disease was admitted in our maternity ward with threatened preterm labor. Her past medical history revealed that she was diagnosed to have a double inlet ventricle with severe aortic and pulmonary stenosis, one and a half years back when she was being evaluated for dyspnoea and palpitation with her pre-existing diagnosis of rheumatic heart disease (RHD) with severe aortic stenosis at some other centre. Considering the complexity of surgical procedure (Fontan operation) with subaortic outflow resection and uncertainty of long term outcome with surgery, the patient had refused for surgical correction and opted for medical follow-up.

Her first visit to our antenatal clinic was at 8 weeks of gestation for a routine check-up. She had no complaints except for dyspnoea (NYHA class II). Physical examination revealed clubbing of fingers (Figure 1) and cyanosed lips, nose and tongue. Her oxygen saturation (SpO2) was 84% and heart rate was 64 beats/minute. On auscultation S1 was normal S2 single; ejection systolic murmur of grade 3/6 was heard at left 2nd intercostal space. Her baseline echocardiography showed a double inlet single ventricle with intermediate morphology, malposed great vessels both arising from the rightward aspect of single ventricle, large

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ventricular septal defect (VSD), severe subvalvular aortic stenosis and severe valvular pulmonary stenosis with peak gradient of 10 mmHg. The systolic performance of a single ventricle was conserved (ejection fraction= 60%). Rest all investigations were within normal limits. A fresh Echocardiography was repeated that showed the similar findings and there was no deterioration in ejection fraction or development of pulmonary hypertension. The family was counseled about the complexity of the condition and associated poor prognosis, but they decided to continue the pregnancy. Ultrasonography confirmed a single live intrauterine pregnancy of 8.3 weeks. Following this, she had regular antenatal visits along with cardiological assessment. Despite the severity of her disease, she had an uneventful antenatal period. Anomaly scan at 20 weeks showed no gross anomaly in fetus. Fetal echo at 28 weeks was normal but there was evidence of asymmetric intra uterine growth restriction (IUGR) with normal Doppler.

On admission at 32 weeks for threatened preterm labor she was managed conservatively & steroids were given for pulmonary maturity. Her hemoglobin was 11.3 gm% and haematocrit of 41%. An electrocardiogram showed a sinus bradycardia with sinus rhythm, ST changes in lead V1, V2, V3; left axis deviation with intraventricular conduction defects (Fig. 2). Repeat sonography revealed high resistance flow in umbilical arteries and moderate oligohydramnios. She was taken up for an elective caesarean section at 33.4 weeks period of gestation under antibiotic coverage & epidural anaesthesia & delivered an alive male baby of weight 1.7kg & APGAR 8/10 at 1 min. Intra operative period was uneventful. The estimated blood loss was 600ml. Pain relief was achieved with epidural top ups followed by paracetamol infusion. She had atonic PPH one hour after the caesarean which was managed conservatively and one unit packed cell volume was transfused. In the post operative period, her oxygen saturation remained between 74% - 80% in room air. She was given intermittent humidified oxygen to maintain her saturation. Anti-coagulation with low molecular weight heparin was started eight hours after surgery for prophylaxis against deep vein thrombosis and replaced by oral anticoagulants from the fourth day.

Echocardiography of the newborn was normal. She was discharged on 10th post operative day in satisfactory condition. She has been under regular follow-up for last one year and is in good condition.

Discussion

Cardiac diseases in pregnant women are now increasingly encountered in our clinical
practice. With recent advances in the field of pediatric cardiac surgery and improved childhood survival, there is a rising trend in the population of reproductive age women with congenital heart diseases. Most of these women, especially those with lesions of moderate or severe complexity, have sequelae that increase their risk of cardiovascular complications during pregnancy (3).

Univentricular heart or double inlet ventricle is a rare congenital cardiac anomaly, characterized by a large dominant ventricle, most commonly, a morphological left ventricle while the other ventricle is a small rudimentary chamber. Patients with a functionally single morphological left ventricle with a well balanced circulation i.e. some degree of pulmonic stenosis to avoid excessive pulmonary blood flow, may achieve late survival with good ventricular function, exercise capacity and minimal symptoms (4). Our patient had severe pulmonary stenosis which was good for her as it prevented the development of pulmonary hypertension. Unoperated cases of univentricular hearts have poor prognosis with a median survival of 14 years (death rate of 4.8% per year) and with majority of patients presenting with cyanosis and decreased exercise tolerance (3). Pregnant women with cyanotic CHD are at increased risk for maternal and neonatal complications. Fortunately, as long as their ventricular function is normal they tolerate pregnancy well. Maternal heart failure, pregnancy induced hypertension, pulmonary oedema, endocarditis, arrhythmias, embolism, stroke, hemorrhage, thrombosis, and maternal death are the risks encountered in these pregnancies (5). In uncorrected pregnant patients with cyanotic CHD the usual pregnancy associated fall in systemic vascular resistance and rise in cardiac output exacerbate right to left shunting leading to increased maternal hypoxemia and cyanosis (6). Fetal complications such as premature births, small for gestational age, low birthweight and respiratory distress syndrome are often associated with univentricular heart disease (5).

Our patient also presented with preterm labor and the baby had IUGR.

Since such patients are prone to maternal and fetal complications, they should ideally be managed in a tertiary care centre with a fully equipped cardiac care unit (CCU) and round the clock availability of a cardiologist, anaesthetist and obstetrician. Our hospital was the only tertiary care hospital in the Andaman & Nicobar group of Islands where people used to come from far off places & remote islands either by ships or by helicopters. The hospital had a good medical and surgical intensive care unit with almost all the facilities but unfortunately there was no CCU and cardiologist at that time. Patient was therefore advised referral to the mainland but she refused to go. However she could be well managed by the combined efforts of physician, anaesthetist and the obstetricians. The favorable outcome reported in our patient was probably due to the absence of pulmonary hypertension.

A study by Presbitero et al. examining the outcomes of 96 pregnancies in 44 women with a variety of cyanotic CHD reported a high rate of maternal cardiac events (32%), including one mortality, prematurity (37%), and a low live birth rate (43%) (7). The main determinants of live birth were the arterial oxygen concentration at rest (>85%). They concluded from the study that women with cyanotic CHD can go through pregnancy with a low risk to themselves, with frequent treatable complications, but there is a high incidence of miscarriage, premature births, and low birth weights (7).

Favorable outcomes have been reported following vaginal delivery or caesarean section in women with univentricular heart (8-10). Epidural anaesthesia provides excellent analgesia in the immediate post operative period. All patients must receive antibiotic cover and thromboprophylaxis during their hospital stay or until they achieve full mobilization (10). Moreover preconception counseling should be emphasized so as to allow women to make informed pregnancy decisions and risk
stratification tool can be helpful to predict pregnancy risk.

**Conclusion**

Pregnancy is often well tolerated in a single ventricle patient with good NYHA functional class, good ventricular function and an oxygen saturation > 85%. The risk of paradoxical emboli in these patients is high and meticulous attention should be paid to avoid deep venous thrombosis in these patients.

**Declarations**

Authors declare no conflict of interest.

**References**


Mini Review

Biosensor Designs for Platelet-derived Microparticles Analysis

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ABSTRACT

Platelet-derived microparticles (PMPs) are often used as marker of platelet activation and their count in blood has been found to be significantly associated with many diseases like myocardial infarction, stroke, venous thrombo-embolism etc. PMPs have been proposed as potential biomarkers for these conditions. Biosensors are newer analytical tools, being developed for convenient and cost effective analysis. For PMPs analysis, biosensors offer many advantages over conventional analysis techniques. This mini review compiles designs and techniques of reported biosensors based on antibody capturing for analysis of PMPs.

Keywords: Platelet-derived microparticles, biosensors, biomarkers, electrochemical analysis, myocardial infarction.

Introduction

Platelets release extracellular vesicles (EVs) in blood. Vesicles originating from cell membrane budding are known as microparticles while smaller vesicles originating from intracellular multivesicular bodies are called exosomes. Platelet-derived microparticles (PMPs) are often used as marker of platelet activation (1, 2). PMPs are most abundant EVs in human blood (3, 4). PMPs are of heterogeneous in size ranging 0.1 to 1 micron (100-1000 nm), while exosomes size ranges from ~40-100 nm (3). Ninety percent of platelet EV are below 500 nm in size, majority being in range of 100-250 nm (5). PMPs play significant role in cell to cell communication, homeostasis, angiogenesis and other functions. They are rich in phosphatidylinerine, tissue factor and many other receptors and have procoagulant surface and ability to interact with leukocytes and endothelial cells (6-8).

PMPs count in blood has been found to be significantly associated with many acute and chronic diseases like myocardial infarction, stroke, venous thrombo-embolism, preeclampsia, fungal (candida albicans) sepsis, systemic lupus erythematosus (SLE), rheumatoid arthritis, etc. (9, 3, 10-13, 4, 14). Increased number of circulating microparticles can trigger hypercoagulable state, which may lead to thrombo-embolic complications (11).

PMPs play role in haemostasis and are considered highly procoagulant (4, 15). Increased blood PMPs concentration in patients of myocardial infarction and acute coronary syndrome, compared to healthy individuals, has already been reported (16, 10, 17, 15). Thus, PMPs level in blood has been proposed as potential biomarker (18, 10, 17). Multiple techniques for PMPs level estimation and characterization have been reported, including flow cytometry, electron microscopy, nanosight...
tracking analysis, ELISA, etc.

Biosensors are analytical devices that combine biological components with physico-chemical detectors. Biosensors offer many advantages over conventional analysis techniques like low cost, quick results, miniaturization and easy application (19). Immunosensor is a variety of biosensor where principle of antigen-antibody reaction is utilized for specificity of detection and antibodies are fabricated on sensor platform for analyte capture (20). Novel biosensors are being reported regularly and are gaining popularity in medical diagnostic field (20-22). For convenient analysis of PMPs, biosensors are being developed as newer tools.

**Designs of biosensors for PMPs analysis**

Our lab was first to design specific antibody based PMPs capture nano-bio-sensor platform. We reported a graphene oxide based biosensor for quantitative estimation of PMPs. Glassy carbon disc electrodes were fabricated with graphene oxide at first step, then PMP specific PAC1 (first Procaspase Activating Compound) antibody was immobilized onto it to make the sensor specific for PMPs. Detection was based on electrochemistry by frequency response analysis (FRA), which detects impedance applied by immobilized PMPs on sensor surface. The results were compared and confirmed by flow cytometry analysis of same PMPs samples. Our biosensor successfully and quantitatively estimated PMPs levels in plasma samples of healthy donors as well as acute myocardial infarction patients. The detection limit of our biosensor was 100 PMPs per µL sample, and linear response was seen upto 7000 PMPs per µL for quantitative detection. This biosensor design proved to be most suitable for quick, cost effective, sensitive and user friendly point of care testing and opened new paradigm for development of biosensor based PMPs detection techniques (10).

In 2017, building upon our PMPs biosensor technique, Singh *et al.* reported another design of biosensor based on nanosilica-PAC1 antibody, P-selectin antibody and conjugated Horse Radish Peroxidase (HRP) on ITO (Indium Tin oxide) electrode (23). Thionine doped silica nanoparticles were synthesized and applied for this biosensor design, where Nanosilica was used as 3-dimentionals platform for biomolecules encapsulation and thionine was used as mediator of electron transfer. PAC1 antibody was used for capturing PMPs on sensor surface, while HRP tagged P-selectin antibody generated detection signal after reacting with H2O2 (hydrogen peroxide). Signal generated by H2O2 oxidation through HRP tagged P-selectin was used for estimation of PMPs quantity. H2O2 oxidation was detected by cyclic voltametry, where higher concentration of PMPs in sample generates higher peaks in cyclic voltamograms, which in turn successfully detected PMPs numbers in samples. Reported detection limit was 490 PMPs per µL sample, and linear response was seen upto 4080 PMPs per µL (23).

A hybrid technique for simultaneous real time quantification and characterization of PMPs by combining surface plasmon resonance (SPR) and atomic force microscopy (AFM) was also developed and reported as an 'on-chip' NanoBioAnalytical platform in 2017 (24). Authors immobilized CD41 antibody on gold sensor chip to capture PMPs, and then used SPR and AFM to characterize captured PMPs. This technique eliminated size limitation, need for labelling PMPs and complex sample preparation. This technique allowed metrological analysis of captured PMPs and revealed that more than 95% of PMPs were smaller than 300 nm. This method reported analysis of PMPs of size range 30 nm to 1 µm and concentration range 10^9-10^10 per µL (24). Results suggested that this NanoBioAnalytical platform, combining SPR and AFM, is a suitable method for a sensitive, reproducible, label-free characterization and quantification of various microparticles over a wide concentration range (24).
Biosensor based techniques offer many advantages by reducing analysis time, eliminating staining steps, ease of application and requirement of very small sample volume for detection. These biosensors are still under development phase, targeted for user friendly wide spread applications.

References


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