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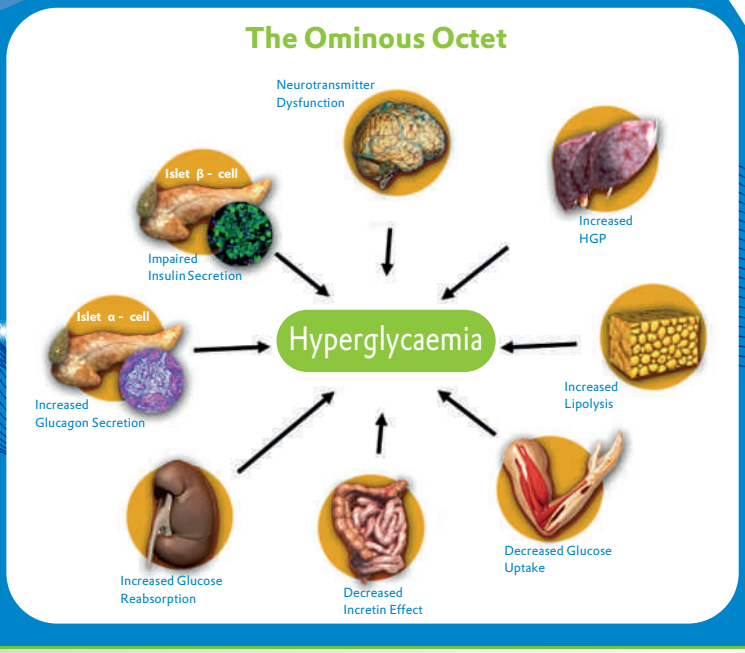
MEDICAL JOURNAL

In this issue



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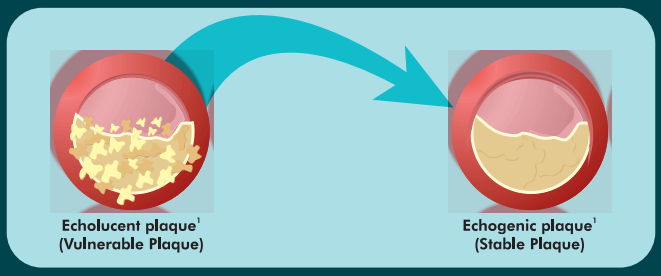

1. Atherosclerosis 215(2011) 440-445. * Coronary Artery Disease MA/CV/SXL/ADV/019/Mar 2012 Not to be used beyond Feb 2014 For the Use only of a Registered Medical Practitioner or a Laboratory or a Hospital

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Chettinad Health City

MEDICAL JOURNAL

Contents

Editorial

Vanakkam. The current issue of the journal features Prof Venkataswami, the pioneer of hand surgery in India in the section- 'Dialogue with a stalwart.'

This issue of the journal carries several interesting articles. The perspective article on Evolution and Medicine, gives a new insight to many of the commonly observed events in clinical practice. It helps us understand the concept of 'Beneficial dirt.'

An original article describes the predictors of adverse outcome in asphyxiated and ventilated late preterm and term newborns. Another original article describes a novel tool for sex determination by Cheiloscopy and Palatoscopy.

The pandemic of Diabetes is addressed in a special section. Life style is the major contributor for the increasing incidence of Diabetes. Diabetes affects all walks of life and all the organs and systems in the body. This section was co ordinated and edited by Dr R. Bharath, Consultant Endocrinologist.

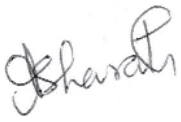
Diabetes mellitus has become one of the most common non-communicable diseases worldwide. Its exponentially growing incidence, chronicity, predilection to affect the major organs in the body and the enormous health care expenditure involved have altogether made diabetes a "pandemic". The shift from the era of food scarcity to food sufficiency in most of the developing countries including India, "Westernized" food habits, sedentary lifestyle and increasing psycho-social stress contribute to the emergence of obesity which ultimately leads to diseases like diabetes mellitus, hypertension, dyslipidemia and cardio vascular diseases. In the last few decades, major path breaking research has been done in diabetes mellitus. These efforts focused mainly on understanding the complex patho-physiological mechanisms of the onset and progression of diabetes and translating the results to patient care. Consequently, the therapeutic armamentarium of diabetes mellitus has expanded to include newer drugs which target certain "unmet needs" in diabetes management. Insulin itself has undergone various modifications to make it more flexible with more physiological action profiles and reduced risks of hypoglycemia. Management of diabetes in special situations like in children & adolescents, pregnancy, patients with cardiovascular disease and critically ill patients needs a pragmatic approach. The war against diabetes can be won only with the help of a team approach involving the patient, his or her care givers, medical professionals and the community. Creating knowledge and awareness among the medical practitioners and general public is the corner stone of success of any Diabetes care team.

A case report describes synchronous presentation of sporadic angiomyolipoma and renal cell carcinoma. Another case report describes Peripheral Giant Cell Granuloma of the gingival tissue.

The pages of history take us to France to witness the development of Rabies vaccination. The Medical update column describes the role of the 'good bad and the ugly' cholesterol, besides several other useful information.

The journal completes one year with this issue. The journal became a reality due to the great support we received from the management and the administration and the unstinted support from the authors, peer reviewers and the readers. The core committee and the editorial board of the journal places on record it's gratitude to all those who made this possible.

The journal has touched upon several important areas of medical practice in the last one year. We had a good mixture of medical, surgical, gynaecological and dental articles. We hope you will enjoy going through this issue of the journal. Do give us your valuable feed back.



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Perspective Article

Evolutionary Medicine: Seeking a Fuller Understanding of Disease

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After obtaining his B.Tech in Industrial Biotechnology from Anna University (Guindy), Dr. Ashok chose to decline admission to IIM-Calcutta, instead to pursue doctoral studies at the Beckman Institute of Advanced Science and Technology, University of Illinois at Urbana-Champaign, USA. His thesis involved biophysical investigations of ion channels in excitable membranes (2005). After a stint at Rajah Muthiah Medical College, Chidambaram, he joined C.H.R.I. in March 2010. His interests concern a quantitative basis to the applications of evolution to problems in biomedical science.

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Abstract

Evolutionary medicine is concerned with the rational understanding of diseases, and the application of this understanding to the prevention and treatment of disease, and betterment of public health. Fundamentally, there are three reasons suggested by evolutionary medicine to account for the origins of disease: 1. Natural selection is slow - our bodies are in an environment to which we were not adapted; in addition, we are competing with faster evolving pathogens. 2. Selection is constrained: every trait is a trade-off, and none can be perfect for all aspects; moreover, natural selection must work with existing situation and possibilities, and cannot recover a path that has been forsaken and lost. 3. We misunderstand: organisms are selected for reproductive success, and when the peak reproductive period is past, individual strength and health decline. Further, we mistake the utility of evolved defence responses like fever, pain, and anxiety, which may cause suffering, but are important in the preservation of life. An evolutionary perspective provides a fascinating understanding of previously baffling areas of human health and disease.

Key Words : Evolutionary theory; maladaptation; causes of disease; antagonistic pleiotropy; auto-immune diseases; pathogen evolution; cancer.

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Introduction

Medicine is generally about the reckoning of mechanistic details, but it rarely deals with the nonmechanistic basis of health and disease. To take one example, we might wonder about the causes of ageing, and settle for an unsatisfactory understanding: Things wear out and maybe natural selection is not great. There is resistance to the introduction of evolution into the medical curriculum. The point of view of evolution would aid understanding the whys of aging. Evolution is simply a basic science that is highly relevant to many subjects in medicine. An approach that assures immediate interest from medical students is to begin by placing the human species in an evolutionary context[1].

Biological causation

Much of biology is focused on the physical and biochemical mechanisms underlying the immediate causes of traits or processes. For e.g., how does the adaptive immune system recognize foreign material? Physiology, biochemistry, genetics, development, and related fields concentrate on such proximate causation. Evolutionary biology tends to focus on ultimate causation, i.e. on understanding how natural selection, evolutionary conflicts, and historical events have shaped the trait under consideration on a timescale of many generations. It is clear that two kinds of explanations are needed when dealing with deep questions. The first is proximate explanation, which is what we usually encounter in the study of medicine, and the second kind of explanation is the understanding of ultimate causation. This leads to an evolutionary understanding of the trait or phenomenon and is aptly referred to as evolutionary explanation[2]. The importance of evolutionary causes was stressed by E.Mayr[3]: "No biological problem is solved until both the proximate and the evolutionary causation has been elucidated. Furthermore, the study of evolutionary causes is as legitimate a part of biology as is the study of the usually physico-chemical proximate causes."

Evolutionary medicine

A tenet of evolutionary theory is that when inheritable variations in a trait alter the fitness of the organism, natural selection will act on the trait to change and improve over the generations. T. Dobzhansky had remarked[4]: "Nothing in biology makes sense except in the light of evolution." While that statement is justified, we should be wary that not all evolutionary explanations make sense. Clearly, evolution is the foundation for biology; in turn, biology is the foundation of medicine, which makes the connection between evolution and medicine deep and essential. This connection itself is a vibrant discipline, called evolutionary medicine[5,6].

Evolutionary medicine evaluates medical problems in the background of evolution. It is concerned with understanding why we are vulnerable to a host of maladies in the modern age, chief among them emerging infections, cancer, back pain, apnoea and prenatal complications. The physiological design of our body has been subjected to a bundle of pressures, and compromise is inevitable. Explanations for the body's vulnerabilities could be generalized into a few categories, which could aid our understanding of the origins of diseases of modernization.

The origins of disease

The key insight of evolutionary theory for the practice of medicine is that disease itself may not be shaped by natural selection, but vulnerability to disease is certainly shaped by natural selection. The trade-offs and constraints involved in natural selection tend to give rise to maladaptation as often as adaptation[7].

Evolutionary medicine is a historical transition in the understanding of disease. It aims to uncover the origins of vulnerabilities to disease, and how this understanding could be applied to improving disease management and therapeutic outcomes. Evolutionary medicine offers six reasons that we are selected for vulnerability to disease.

Evolutionary causes of disease

1. Mismatch between physiological design of body and novel environment
2. Competition with fast evolving organisms
3. Every trait is a trade-off
4. Constraints on natural selection
5. Organisms shaped for reproductive success, not health
6. Defences and suffering

Mismatches to modernity

Prior to 10, 000 years, most humans very likely lived in small groups or tribes of "hunter-gatherers." This is sometimes considered the "environment of evolutionary adaptation" in which most of our genes were selected, across ~5,000 generations. The Paleolithic diet meant that it was useful to have genes that helped store fat; in times of famine, these genes promoted reproduction and survival. This is sometimes called the "thrifty gene" hypothesis. Post-paleolithic human diet has witnessed several changes. In the modern age with the ready availability and superabundance of fatty, high-sugar and high-salt foods, the "thrifty" genes do not continue to perform a useful function. They are maladaptive in the modern environment and are implicated in the genesis of lifestyle diseases like obesity, atherosclerosis, and diabetes. The reasoning is supported by the increasing incidence of metabolic syndrome and diabetes in populations that were agrarian for a long time (e.g., we South Indians).

Further the industrial age has fostered behavioural changes affecting the incidence of disease. The toughness of food is reduced to make chewing easier and this may be associated with less gingivitis. The real consequences of the loss of toughness of food are the adverse (reduced) jaw size, dental crowding, and impacted molars. Another dramatic change is the alteration of the female reproductive schedule, with the attendant implications for disease. In earlier times, most women had relatively large numbers of children (many of whom did not survive). There is an increasing frequency of women having either no children or one late child, which constitutes a major risk factor for breast and ovarian cancer.

A key medical concern of our cultural evolution is the increasing risk of autoimmune diseases, referred to as the "hygiene hypothesis". The success of epidemiology and public health in reducing infections has played a role in increasing human longevity. On the other hand, the need for increasing cleanliness to be adopted for this success story has left our microbiomes and our immune systems in a state vulnerable to infection, in which allergies, auto-immune diseases and unexplained disorders like inflammatory bowel disease appear to increase in incidence. Evolutionary medicine provides a key insight for this phenomenon: The development of our immune system co-evolved with worms and bacteria. When modern hygiene and antibiotics acted against the worms and bacteria, our immune systems developed inappropriately. It is worth observing that as epidemics of infectious diseases are being controlled, the incidence of autoimmune diseases is worsening. These mismatches to modernity are referred to as diseases of civilization.

How do we arrive at a molecular understanding why worm infections reduce allergy risk? Worms had evolved the ability to produce molecules that block or downregulate immune responses that could kill or expel them. The immune response to chronic infection is strong inflammation, but since inflammatory responses are damaging and debilitating, selection shaped hosts to decrease the intensity of immune response to worm infection. Thus both worms and humans have evolved to reduce inflammatory responses. A few clinical observations in this direction are worth mentioning. Farm children have fewer allergies than city children. Schoolchildren with schistosomiasis have fewer allergic reactions to dust mites. Adults have less asthma when infected with nematodes.

These observations lead us to wonder about the utility of therapies that could restore our microbiomes and enable the proper development of the immune system. Does deliberate worm infestation confer protection against auto-immune disease? A research therapy involving deliberate infestation of ova of pig whipworms has yielded significant positive outcomes against Crohn's disease and ulcerative colitis, and independently against multiple sclerosis[8,9]. There is much to look forward to in terms of practical therapies of previously untreatable diseases, including exploring whether we would be able to devise therapies that mimic the interaction of living worms with the developing immune systems.

Competition with infectious organisms

Evolutionary medicine suggests a Darwinian approach to signs, symptoms and treatment of infectious disease. Infectious agents maximise their ability to survive and reproduce despite elaborate host defences. Further, parasites interact with hosts in complex ways and it's helpful to break down phenomena associated with infectious disease.

Observable	Beneficiary
Direct damage to host tissues	Neither
Repair mechanisms	Host
Compensatory adjustment to impairment	Host
Hygienic measures	Host
Host defense	Host
Evasion of host defenses	Pathogen
Pathogen dispersal mechanisms	Pathogen
Pathogen manipulation of host adaptation	Pathogen

Darwin's theory of evolution is a comprehensive body of evidence that attempts to explain the gradual evolution of life on the planet, and their descent from a common ancestor. Among the many applications of evolutionary biology, some representative ones to the understanding of infection[10] include:

- HIV retrovirus which is of enormous medical concern: Because of evolutionary studies, we know that two separate lineages of this retrovirus passed into the human population from African Apes in the mid 20th century. This knowledge has alerted us to the danger of emergent diseases from other animal hosts (the phenomenon of zoonosis), a reason for our concern about SARS and avian flu. It is also the understanding of evolutionary biology that has enabled us to develop a therapy for HIV – the so-called "triple therapy" HIV treatment. A single drug will not work against the disease because the virus evolves so quickly, it attains resistance within a few months.

- Acquisition of antibiotic resistance is an evolutionary phenomenon that has turned into a huge medical problem. Resistant pathogenic bacteria evolve in response to the inappropriate or extensive use of drugs. Many antibiotics, such as penicillin, were evolved by fungi, over millions of years, to kill off their bacterial competitors. We have co-opted them for our own purposes. Extensive use of these drugs has caused very strong natural selection for mutations which favour antibiotic resistance. Evolutionary medicine informs us that we should limit the doses of antibiotics we use for long periods, and rely on a dosage no larger than is absolutely necessary to control infections. Further, research on the genotyping of infectious strains could enable us to devise better treatment for emerging diseases.

Defences and suffering

Evolved defences such as pain, fever, nausea, and diarrhoea can cause suffering, but may also respresent beneficial responses and/or early warning signals of pathology. This is known as the "Smoke detector principle." A single alarm is usually a false positive, but costs little. On the other hand, missing out on a true positive could be fatal, and the alarm in this case is worth the discomfort.

Could fever be an adaptive response?

Many people consider the symptoms of illness to be a nuisance. It would be interesting to know why fever tends to occur when we are sick. One possibility is that fever may represent manipulation of the host by the pathogen. Or, fever may be an adaptive defense against the pathogen, which interferes with its reproduction. Fever may also serve to enhance the immune response against the pathogen. It is pertinent to recall the work of Julius Wagner-Jauregg (1857-1940) who noted that some neurosyphilis patients improved after getting malaria and that such syphilis was rare in areas where malaria was common. After intentionally infected thousands of syphilis patients with malaria, Wagner noticed that remission rates for syphilis increased from less than 1 percent to 30 percent. Wagner won the 1927 Nobel Prize for medicine for this work ("for his discovery of the therapeutic value of malaria inoculation in the treatment of dementia paralytica"[11]). Fever is a highly regulated response triggered by the release of "endogenous pyrogens". With the widespread use of antipyretic drugs, we seem to favour 'feeling better' over the benefits of immune response.

Trade-offs and constraints

Compromise is inherent in every adaptation. More sensitive ears might sometimes be useful, but we would have to cope with the noise of even air molecules impinging on our eardrums. Arm bones three times their current thickness would almost never break, but the upkeep of heavy bones would require that we are forever searching for calcium. Such trade-offs also exist at the genetic level. Ageing may be the ultimate example of a genetic trade-off when the force of selection is stronger in youth.

Secondly, evolution can take place only in the direction of time's arrow. This means that the evolution of an organism's design is constrained by existing and pre-existing structures. The vertebrate eye is arranged backward, with the optic nerve in front of the retina, which results in the blind spot. However, the squid eye does not suffer this defect, because vessels and nerves only run on the outside, preventing detachment of the retina by selectively penetrating and pinning it down.

It is the consequence of evolution that the simple act of swallowing can be life-threatening. Our respiratory and food passages intersect due to the legacy of early lungfish ancestor. We seem 'stuck' with the appendix,

which played an important role in digestion, today reduced to a vestigial adaptation. Not only is the body not perfect, but an evolutionary analysis reveals that we do live with vulnerabilities, some of which are necessary for the survival of the organism. Let us revisit the question we earlier posed from an evolutionary perspective: could we explain ageing? Any mutation that improves reproductive fitness (and expressed early in life) will be selected even if it would reduce the lifespan of the organism. Such mutations produce a coupling of traits expressed early and late in life and contribute to the evolution of senescence[12]. A genetic coupling of traits with trade-offs in ageing is called antagonistic pleiotropy.

Cancer as Evolutionary Process

Every cancer is an independent evolutionary process. Tumour clones originate through somatic mutations, and selection operates on the genetic heterogeneity of clones. Cancer increases mutation rates and evades the immune system surveillance. The malevolence of cancer is aggravated by the potential for metastasis, by which a cancerous clone spreads from its locus, and invades and colonises neighbouring body organs. The evolution of a neoplasm bears a parallel to natural selection. There is variation in the population of cells, this variation amongst the cells is heritable, and this heritable variation affects reproduction and survival of the cells. Cancer is essentially evolution in action, albeit deleterious to the host. Why are we afflicted with cancer? Again we seek an evolutionary explanation, not just the proximate cause. We now survive much longer than we did on average in the evolutionary past, well into post-reproductive ages. The evolution of cancers resistant to chemotherapy can be managed by restricting the doses used in chemotherapy. This strategy, which is the outcome of evolutionary thinking to delay the emergence of malignancy, must be improved with model systems and large clinical trials to convince clinicians and patients that high doses are not necessarily better doses.

Conclusion

The general message is that genomic claims of simple genetic determinism are ill-founded and misleading. There is no credence to a notion of "the normal body". I hope that this overview of some of the main ideas of evolutionary medicine has emphasized the critical importance of teaching evolution to medical students. It is our duty to future generations of physicians and patients to ensure that this fundamental keystone of biology takes its due place in the medical curriculum. The modern diminution in early deaths arising from malnutrition, infectious disease, and trauma has greatly increased the number of individuals living well beyond the reproductive phase, and generates social, fiscal, and medical issues related to ageing. The apparent human evolutionary propensity for longevity has huge implications for the future of medical practice.

Acknowledgement

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Original Article

Predictors of Adverse Outcome in Asphyxiated and Ventilated Late Preterm and Term Newborns

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Abstract

Objective; To assess the factors that modify the outcome among asphyxiated out born babies who needed ventilation in a tertiary care centre within 24 hours of life. **Study design;** Observational cross sectional study **Setting;** Extramural tertiary care neonatal unit, **Subjects:** Asphyxiated neonates of gestational age>34 weeks requiring ventilation **Methods;** 114 asphyxiated neonates were included in the study. Data regarding antenatal risk factors, delivery, stabilization and transport details, status of the baby on admission, course in hospital including time of initiation of ventilation and duration of ventilation and final outcome was obtained, Nested case control design was used to analyse and identify risk factors which modify outcome. **Results;** Adverse antenatal factors, p 0.02 OR 2.49(1.07 -5.85) low birth weight, [p 0.001] OR 5.78(1.62-21.68) and admission within 6 hours was found to be statistically significant as a predictor of poor outcome [p 0.02] 2.50(1.03-6.09) Hypothermia [p 0.04] OR 2.17(1.00 – 4.80)] on admission was also associated with a poor outcome. **Conclusion;** Lack of Pretransfer stabilization before transport increases the mortality among asphyxiated neonates. Pretransfer stabilization is absolutely essential in neonates before transport to referral centre

Key Words : Out born neonates; Asphyxia; Ventilation; Outcome

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Introduction

India accounts for 30 per cent of the neonatal deaths globally. In India, the neonatal mortality rate is 33/1,000 live births.[SRS 2010] Most of these deaths occur within the first days of life. 46.2 per cent occurring in the first two days of life and 73.3 per cent taking place within the first week of life.[Million Death Study, Lancet 2010][1] Sepsis and asphyxia are the major causes of death among extramural births. It has been estimated that health-facility based interventions can reduce neonatal mortality by as much as 25-30% (Lancet 365:977-88.] when problems are identified and managed early. This study was embarked upon to assess those factors that determine an adverse outcome among asphyxiated babies who needed ventilation and were referred to a tertiary level centre within 24 hours and also to identify modifiable factors affecting the outcome in case of asphyxiated neonates which may have an impact on bringing down the Neonatal mortality rate. Anticipation, recognition of problems and early referral of asphyxiated newborns to higher centers has been reiterated in several studies but this study emphasizes the need for proper stabilization before transfer and during transport to higher centers in order to ensure optimum survival of asphyxiated newborns.

Material and Methods

This observational study was conducted in the extramural Neonatal unit of the Institute of Child health, Chennai, Tamil Nadu. After obtaining the approval of our Institute review board, Madras Medical College the study was conducted over a nine month period (November 2010 –June 2011]). 114 Neonates of gestational age>34 weeks with asphyxia [based on referral diagnosis and clinical features] who were admitted within 24 hours and who required ventilation were included in this study. The details of the mother and the baby [parity, sex, birth weight] place of delivery, mode of delivery, and immediate postnatal events like Apgar score, resuscitation done, and other management given were recorded The mode of transport, temperature, capillary blood glucose [whenever available] and capillary refill time of the newborn at arrival were recorded. The respiratory distress score by Downe and oxygen saturation by pulse oximetry were also noted in the emergency room. All babies were treated based on standard management protocol. The, mode, duration and complications during ventilation were recorded. Parents were counseled though out their stay regarding the prognosis and disease progress. The outcome in each case was also noted and advice regarding follow up was given at discharge and in cases of death the parents were counseled to deal with grief. Results were analysed using the chi-squared test

Results

Out of the 114 babies who were included in the study, 65 babies survived and 49 died. Analysis of factors prior to birth [Table 1] revealed the presence of antenatal adverse factors in 34 of the discharged babies and in 31 of the babies who died [p 0.02] 2.49(1.07-5.85]. While 31 of the discharged babies and 18 babies who died had no antenatal risk factors in the form of prolonged 2nd stage of labour and meconium stained amniotic fluid. 78% [n=89] of the deliveries were in the State Health Facility with a small contribution from the private hospitals. Normal vaginal delivery was the type of delivery observed in 74 [65%] cases. Transport of the high risk babies was done by both Government ambulances [65%] and private vehicles [35%]. Place and type of delivery and the mode of transport did not affect the outcome. Considering the factors after birth,[Table 2] there were 76 males and 38 females in this study with majority of them being delivered at term[95%] 75 babies belonged to the average weight group, mortality being higher in the low birth weight group [p 0.001] 5.78(1.62-21.68).When the time of admission was taken into account[Table 3], it was found that those babies who were admitted within 6 hours of life had a higher mortality [p 0.02] 2.50(1.03-6.09). 73 [64%} babies were normothermic on admission and [45%} babies were hypothermic 77 [67%] babies had normal capillary glucose levels at admission, while 15 babies were hypoglycemic. Severe respiratory distress was present in 18[16%] of babies, while 56[50 %] babies were apneic! 76[66%] babies required intubation on arrival. Shock was observed in 66 [58%] babies. Babies were ventilated for varying periods ranging from 6 hours to more than one week. Cause of death in these babies was due to, HIE - 63% MAS/PPHN-27% Sepsis 10%

Discussion

Perinatal asphyxia continues to contribute to nearly 20% of the neonatal mortality rate. With the increase in institutional deliveries the rate of asphyxia should see a decline instead of remaining static. Factors which can be modified so as to minimize the impact of asphyxia at birth were identified in this study.

In this study it was observed that mothers who had problems during labor in the form of prolonged second stage and meconium stained liquor had higher neonatal mortality which was statistically significant [p 0.02] OR 2.49(1.07 -5.85) .This is comparable to the study by Christina et al[2] Since these deliveries were not in a tertiary level unit the incidence of maternal infection could not be assessed unlike the study from Estonia,[3] where maternal infection was associated with birth asphyxia. It was reported that caesarean sections were associated with increased respiratory morbidity [4].This was noticed in this study but it was not statistically significant.

Since only babies which were more than 34 weeks were included in the study gestational age did not contribute to the outcome but babies with low birth weight had higher mortality as in earlier studies[5,6] [p 0.001] OR 5.78(1.62-21.68)

Admission within 6 hours was found to be statistically significant as a predictor of poor outcome. [p 0.02] 2.50(1.03-6.09).This is unlike other studies[7-9] where early referral had better outcome. This could be due to the fact that these babies were transported before any pre transfer stabilization. The time for transfer varied from 30 minutes within the city to more than 4 hours from outside the city. The importance of pre transfer stabilization cannot be over emphasized as evident in multiple studies[10-12] Stabilization before transfer comprises two phases: (a) from when a decision to transfer is made until the transfer team arrives, during which care is delivered by the local staff; (b)during transport to the referral centre. The aim in both of these phases is to resuscitate and stabilize the infant till he reaches the referral point.[10]

Hypothermia [p 0.04] OR 2.17(1.00 – 4.80) at the time of admission which was a statistically significant predictive factor[13] also showed that these neonates were not stabilized before transfer and were rushed to the higher level of care. It was not possible to come to a conclusion about hypoxia, because we could not record pulse oximetry values in all cases. Severe respiratory distress and apnea on admission were present in 65% of babies and 76 [66%] babies had to be intubated on arrival. Airway management should have been done before referral.

Cause of death in these babies were due to, HIE iii - 63% MAS/PPHN-27%. Sepsis 10% .This is comparable to other studies[13,14]

Conclusions

Since antenatal risk factors may not be modifiable at a late stage, antenatal women who are at high risk should have access to tertiary neonatal care centers before labor since intra uterine transfer is the best option. Supervised care during labor will also reduce mortality among low birth weight babies. Prevention and early management of asphyxia in neonates is associated with an optimum outcome as studies have amply demonstrated. Although there is a need for early referral of asphyxiated neonates, they should be stabilized before referral to ensure complete recovery. In addition to the training imparted for neonatal resuscitation and management, training in pre transport stabilization and care during transport should also be imparted to staff at health care facility. This study highlights the need to train the health care providers to manage airway, blood glucose levels and temperature management. All neonates should be transported in controlled environment which necessitates fully equipped Ambulances available with trained staff. Ultimately the retrieving team should consist of a Medical officer trained in the management of neonates and a Neonatal Nurse Practitioner. Further large multicenter studies are required to include inborn errors, anomalies and blood chemistry to assess the cause, course and outcome of Neonatal admissions.

Tables

Table 1 Antenatal factors affecting outcome n=114 Discharged 65 Death 49

Variable		Discharged	Death	Chi square	p value	OR
AN risk factors	Presence	34	31	X2=5.37	0.02	2.49(1.07-5.85
	Absence	31	18			
Place of delivery	GH	21	13	X2=7.16	0.20	
	PHC	14	15			
	Corp	15	6			
	Private	13	12			
	ESI	02	1			
	Med college	0	2			
Type of delivery	Normal	42	32	X2=1.09	0.54	
	CS	14	13			
	Others	09	04			
Transport	EMRI	36	31	X2.0.72	0.69	
	Govt ambulance	05	03			
	Private vehicle	24	15			

Table 2 Factors affecting outcome n=114 Discharged 65 Death 49

Gender	Male	40	36	X2=1.79	0.18	
	Female	25	13			
Gestational age	Term	60	48	X2=2.13	0.54	
	35wks	1	0			
	36wks	3	1			
	37wks	1	0			
Birth weight	1.5-2.5kg 2.5-3kg >3kg	5 53 7	12 23 14	X2=10.27	0.001	5.78(1.62-21.68) 1 3.75[1.28-11.15]

Table3 Admission parameters affecting outcome n=114 Discharged 65 Death 49

Time of admission	<6hrs	44	34	X2=5.4	0.02	2.50(1.03-6.09)
	6-24hrs	21	15			
Temperature	Normal	43	30	X2=4.39	0.04	2.17(1.00-4.8]
	hypothermia	22	29			
	hyperthermia	0	0			
Spo2	Not recorded	09	15			
	Normal	22	20	2=3.24	0.07	0.45(0.17 -1.18)
	hypoxia	34	14			
CRT	Normal	27	23	X2=0.33	0.56	
	prolonged	38	26			
CBG	Not recorded	10	07	X2=3.98	0.26	
	Normal	47	30			
	hypoglycemia	07	08			
	hyperglycemia	01	04			
Respiratory distress	No RD	13	07	X2=6.56	0.09	
	Mild-mod	09	11			
	Severe	06	12			
	Apnea	37	19			
Seizures <24hrs	Presence	32	29	X2=1.11	0.29	
	Absence	33	20			
Intubation in ER	Presence	47	29	X2=2.17	0.14	
	Absence	18	20			
Vent hours	6-24hrs	14	11	X2=3.38	0.33	
	1-3days	18	19			
	4-7days	23	10			
	>7days	10	09			

Table 4 Cause of death n=49

HIE iii	31	63%
MAS/PPHN	13	27%
SEPSIS	5	10%

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A new role for yellow pigment?

We all recognize bilirubin as the haem-derived pigment that imparts an unpleasant yellow colour to those afflicted with certain liver diseases and haemolytic anaemias. But most people fail to realise that it is not a waste product but a powerful anti-oxidant. In a new study carried out in University of Missouri, the researchers discovered that bilirubin could prevent or limit the extent of vascular damage in individuals at risk for occlusive cardiovascular disease. It does so by inhibiting the growth of vascular smooth muscle cells without killing them. However, as bilirubin is not soluble in water and is rather quickly digested when consumed orally,the challenge is to find a way to exploit this useful property of bilirubin therapeutically to check the largest killer. The authors' suggestion: coat the stents with bilirubin. (Frontiers in Pharmacology, 2012; 3 DOI: 10.3389/fphar.2012.00048)

- Dr. K. Ramesh Rao

Original Article

Cheiloscopy and Palatoscopy: A Novel Tool for Sex Identification

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Abstract

Oral and peri oral structures offer a myriad of possibilities in Forensic identification. The importance of dental identification is on the increase year after year. With the passage of time, the role of Forensic Odontology has increased as often teeth and dental restorations are the only means of identification. However, they cannot always be used; sometimes it is necessary to apply different and less known techniques.

Material & Methods: In this study, we analyzed the lip print and palatal rugae pattern in males and females using a classification given by Suzuki and Lysell respectively.

Results: Lip prints and rugae pattern are distinct for an individual. Type 1 and 1' lip pattern were predominantly seen in female subjects while Type 4 and 5 were commonly seen in males. No statistical significant difference was observed in the length of rugae between males and females. A statistically significant prevalence of curve & wavy form were seen in males and straight pattern in females.

Conclusions: Chelioscopy and palatoscopy can be useful in identifying the gender of the person by studying the pattern left at the crime scene.

Key-words: Forensic dentistry, Chelioscopy, Palataloscopy, Sex determination.

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Introduction

Forensic identification by its nature is a multidisciplinary approach relying on positive identification methodology as well as presumptive or exclusionary methodologies which deals with proper handling and examination of dental findings.[1]

Fingerprints and DNA finger printing have been successful in personal identification in the field of forensic science.[2] Just as in these method, lip prints can be instrumental in identifying a person positively and can be used to verify the presence or absence of a person at the scene of crime.[3] External surface of lip has many elevations and depressions forming a characteristic pattern called lip prints, examination of which is referred to as cheiloscopy (cheilos means lips and skopien means see, in Greek) or lip print analysis.[4] The approach is very similar to that of finger print analysis. The pattern of lip print is unique to an individual; hence used in forensic personal identification.

In 1902, the biological phenomenon of systems of furrows and prints on the human lips was first noted and described by anthropologist R.S Fischer. However, until 1950's they were not assumed to have any forensic use. In 1970, Suchhiahashi Y.T and Suzuki.T examined persons lip prints at the department of Forensic Odontology at Tokyo University and established that the arrangement of lines and prints on the lips is individual and unique for each human being.[3,5]

Palatoscopy is the name given to the study of palatal rugae in order to establish person's identity. Palatal rugae are anatomical folds called "plica palatine", the irregular connective tissue located on the anterior third of the palate behind the incisive papilla. As they are stable landmarks, once formed do not undergo any change except in length (due to normal growth) and remain in position throughout person's life. The use of palatal rugae was suggested as one of the method of identification in 1889 by Harrison Allen.[6] The term "Palatal rugoscopy" was proposed in 1932, by a Spanish investigator named Trobo Hermosa.[7] In 1937, Carrea conducted a detailed study and established a method to classify palatal rugae.[8]

Palatal rugae are well protected from trauma by their internal position in the oral cavity and they are insulated from heat by lips, tongue, and buccal fat pads.[9] It is well established fact that rugae retains its shape throughout life and resist decomposition. Personal identification is based on the rugae pattern since the palate would remain intact when most other anatomical structures are destroyed, burned or dehydrated and also in situations where there are no finger prints.

The aim and objective of this study is to ascertain the use of lip pattern and palatal rugae pattern in identification and sex determination.

Materials and Methods

A total of randomly selected 80 subjects comprising of 40 males and 40 females, were selected, their age ranging between 18-35years. All the participants were briefed about the purpose of the study and written consent was obtained from each of the participant.

Inclusion criteria

- Subjects above the age of 18 years
- Lips free from any pathology, having absolutely normal transition zone between mucosa and skin were included in this study.
- Palate free from any pathology and deformity.
  Exclusion criteria
- Subjects with congenital abnormalities /malformation.
- Subjects with surgeries like orthognathic or operation for cleft palate, bony and soft tissue protuberance, active lesions, deformity of scars and trauma to the palate.
- Subjects allergic to impression material or hypersensitive to lipstick.
  Study design

Cheiloscopy: Materials used was

- Brown and red colored lipstick.
- Cellophane tape.
- White bond paper.
- Magnifying lens.

The subjects were asked to clean his/her lips with water and dry them with tissue paper. The subjects were asked to open the mouth and a dark colored frosted lipstick was uniformly applied on the lips up to the vermilion border. Then, the glued portion of cellophane tape strip was placed over the lips and the subjects were asked to make a lip impression in the normal rest position of the lips by dabbing it in the centre first and then pressing it uniformly towards the corner of the lips; The cellophane strip was carefully lifted from the lip from one end to the other, avoiding any smudging of the print. The cellophane strip was then stuck to the white bond paper for permanent record purpose and then analyzed using magnifying lens by three observers. The observers were blinded about the identification and sex of the subjects.

At the time of analysis, the middle part of lower and upper lip was taken as study area in accordance with Sivapathsundaram et al. depends on superiority of properties of the lines on this study area. We followed the classification of lip patterns proposed by Tsuchihashi (1970), which is the most widely used classification in literature.[10]

Type1 : clear cut vertical grooves that run across the lips

Type 1' : similar to type 1, but do not cover the entire lip

Type 2 : branched grooves

Type 3 : intersected grooves

Type 4 : reticular grooves

Type 5 : grooves do not fall any of the type 1-4 and cannot be differentiated morphologically.

Palatoscopy: Materials used was

Alginate impression material

Dental stone

Graphite pencil 0.5

To record palatal rugae, alginate impression of maxillary arch was made and poured with dental stone and casts were preserved for interpretation. The rugae pattern on all the casts was delineated using a sharp graphite pencil under adequate light. The three observers were blinded about the identification and sex of the casts. The information obtained were recorded which included shape and size of the rugae.

A) The rugae pattern was then analyzed on these casts using the classification by Lysell (1955).[11] The rugae were classified based on their size of length as

- Primary: 5mm or more
- Secondary: 3 to 5 mm
- Fragmentary: 2 to 3 mm

B) The rugae were divided into four types based on their shape as

- A= curved
- B= wavy
- C= straight
- D= circular

The three observers were blinded about the identification and sex of the casts. The z-test was applied for the statistical analysis with p value < 0.05.

Results

Lip print

After the interpretation of lip print pattern, it revealed

1. We observed that no two lip print patterns matched with each other (Figure 1)
2. Type 1 and 1' lip pattern were predominantly seen in female subjects
3. Type 4 and 5 were commonly seen in males. This finding is statically significant with P value 0.05 (Table 1).
4. Out of 80, 36 females were correctly recognized as females and 38 males were correctly identified on the basis of lip print.

Palatal rugae

5. In this study, we also observed that palatal rugae pattern of all 80 subjects (Figure 2) were distinct and unique.
6. There was no difference in length of rugae between males and females (Figure 3) which was statistically insignificant.
7. The predominant shape in males was wavy and curved form followed by straight pattern. (Table 2). The circular shape was rare. In females, the straight pattern was predominantly seen followed by wavy and curved pattern.
8. In females, prevalence of Type 1 and Type 1′ Lip pattern with straight form of palatal rugae were seen and In males, predominantly Type 4 and Type 5 Lip pattern with curved and wavy form of palatal rugae was seen

The Z-test was applied to test the significant difference between males and females for different types of lip print pattern, which showed a significant difference for lip pattern 1 ,1′ and 4,5 type (with P□ 0.05).

Applying same test for palatal rugae pattern, a statistically significant prevalence of curve and wavy form was seen in males followed by straight pattern in females.

Discussion

The positive identification of living or deceased persons using the unique traits and characteristics of the teeth and jaws is a corner stone of forensic science. The theory of uniqueness is a strong point used in the analysis of fingerprints and bite marks to convince the court of law. Likewise, even lip prints and palatal rugae patterns are considered to be unique to an individual and hence hold the potential for identification of an individual.[12]

If the gender of an individual is known,[13] it is easier to shortlist the array of suspect for a particular crime. The present study was able to show that lip prints had the potential to identify gender. Although the results obtained in the present study do not prove the method to be infallible, it shows promise in being one more step to get to the truth. Lip prints thus have the potential of being a supplementary tool along with other techniques as a means of reorganization an individual gender. In our study population, Type 2 lip pattern was more frequently found, this finding is in accordance with the studies done in Indian and Chinese population by Manipady et al,[14] while in other studies done by Shivapathsundaram et al[15] in Indo-Dravidian population and by Vahanwala et al[16] in Mumbai population, Type 3 and Type 1 pattern was more common respectively. This difference might be due to Geographical and racial differences.

In this study, we also found that no two lip print patterns matched with each other, establishing the uniqueness of lip prints and is supported by Preethi et al (2007)[8] and Satyanaryana et al (2011).[12]

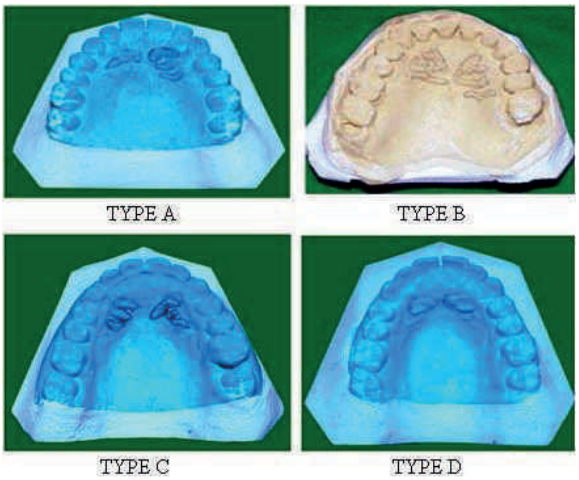

Fig1. Diagnostic cast showing different rugae pattern.

Fig2. Different Lip prints recorded in the given study.

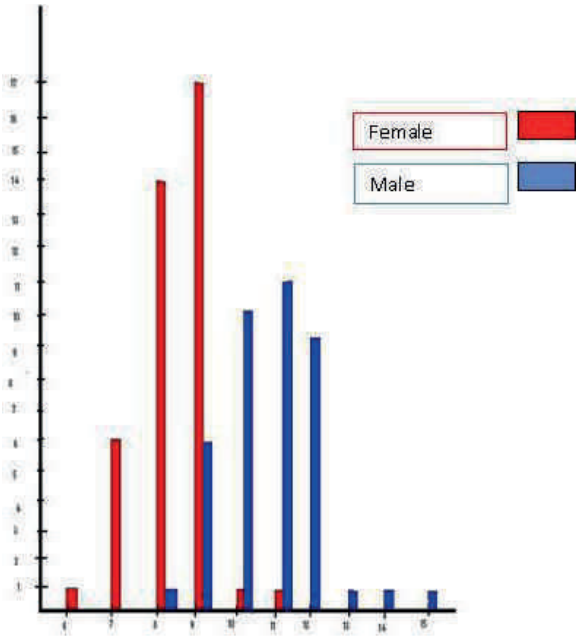

Fig3. Graphical representation of length of rugae in Males and Females.

Table 1: Z test to test the difference in lip print pattern between male and female subjects

Lip print pattern	Males	Females	Z- cal	Z tab		P value
				0.05	0.01	
1	5	11	-1.68	1.96	3.58	<0.01, <0.05
2	0	19	-4.99	1.96	3.58	<0.01, <0.05
3	15	4	2.89	1.96	3.58	>0.01, >0.05
4	8	2	2.03	1.96	3.58	>0.01, >0.05
5	10	4	1.77	1.96	3.58	>0.01, <0.05
6	2	0	1.43	1.96	3.58	>0.01, <0.05

Note:- P>0.05 (Not significant); p<0.05 (Significant) at α = 5% level of significance

Table 2: Z test to test the difference in shape of rugae between male and female subjects.

Rugae Shape	Males	Females	Z- cal	Z tab		P value
1	23	15	1.79	0.05	0.01	<0.01, <0.05
2	14	8	1.50	1.96	3.58	<0.01, <0.05
3	3	16	-3.42	1.96	3.58	<0.01, <0.05
4	0	1	-1.01	1.96	3.58	<0.01, <0.05

Note:- P>0.05 (Not significant); p<0.05 (Significant) at α = 5% level of significance

On one hand, Type 1 and 1' were predominantly seen in female subjects and this is in accordance with the study done by Preeti et al (2007),[8] Satyanaryana et al[12] and Harpreet et al (2011)[2] while on other hand, Type 4 and 5 were more commonly seen in males and is similar to the findings of Preeti Sharma et al (2007).[8] This finding establishes the uniqueness of lip pattern between genders. Due to anatomical position, it is unlikely that the study of palatal rugae could be used in the process of linking a suspect to a crime scene. On the other hand, palatoscopy may be used as a necro-identification technique.

There are different ways to analyze the palatal rugae. Intraoral inspection is probably the most used and economical method. However, this can create difficulties if a future comparative review is required. A more detailed and accurate and the need to preserve evidence may justify the use of photographs or impressions.[3] while observing the shape of the rugae is a subjective process; it is relatively easy to record and does not require complex instrumentation. In this study, we observed that palatal rugae pattern of all 80 subjects were distinct and unique. None of the patterns were identical and also no bilateral symmetry was observed. This finding is in congruity, with results obtained in the studies conducted by English WR (1988),[18] Indira AP et al,[1] Preethi et al (2007).[8]

In this study, curve and wavy form were predominantly seen in males and straight pattern in females which is similar to the findings of previous study conducted by Nayak et al on Indian populations, 13 Valeria et al (2009) in Chile.[17] However, no statistical difference was found in the length of rugae between males and females, this is similar to the studies conducted by Shetty et al (2005). [18]

Conclusion

In forensic odontology, cheiloscopy and palatoscopy is upcoming technique for human identification. Few studies using palatal rugae as a means of forensic identification are found in literature. However, the idea of rugae being unique to an individual is promising and deserves further investigation. The day is not far when cheiloscopy and palatoscopy will be considered important forms of transfer evidence, and shall compliment fingerprints for identification of individual and sex determination.

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Dopplegänger!

Everyone loves high density lipoprotein (HDL) as it protects us against the largest killer - the cardiovascular disease. That is why we call it "good" cholesterol. But the problem with something being so good is that even some undesirable elements begin to covet it. Actually the lymphoma cells love HDL so much that they cannot survive without it. Can their weakness be their downfall? Researchers at Northwestern Memorial Hospital think it is. They have developed HDL gold nanoparticle that behaves like a Dopplegänger (double or look-alike). It looks like HDL but once it is taken up by the lymphoma cell, deprives the cell of its nourishing morsel (HDL) by blocking its uptake. In trials, this nanoparticle without drugs has proved as effective as the chemotherapeutic agents.
(www.northwestern.edu/newscenter/)

- Dr. K. Ramesh Rao

Review Article

Pathophysiology & Management of Type 2 Diabetes: Past, Present and the Future

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Abstract

Diabetes is a metabolic disorder characterized by hyperglycemia resulting due to defects in insulin secretion, insulin action or both. Type 2 diabetes mellitus is the most common form of diabetes worldwide and its incidence is increasing exponentially due to lifestyle changes and increasing prevalence of obesity. Both genetic and environmental factors contribute to its development. Though insulin resistance and consequent beta cell dysfunction have been described as the two basic defects in the development of type 2 diabetes, recent research has thrown light on several other mechanisms including dysfunctional adipocytes, defective incretin action, mitochondrial injury, endoplasmic reticulum stress and defective gut brain axis. Modern management of type 2 diabetes includes lifestyle modification measures; oral anti-diabetic agents aimed at managing different patho physiological aspects of diabetes and insulin therapy in uncontrolled diabetes. Cardio vascular risk factors should also be aggressively treated.

Key Words : Type 2 diabetes, insulin resistance, adipocytes, incretin, free fatty acids

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Type 2 diabetes mellitus is associated with serious microvascular and macrovascular complications leading to higher morbidity and premature mortality. It was considered a condition of minor significance to world health a few decades ago but has become a major concern to public health especially in India with the number of people diagnosed with type 2 diabetes increasing dramatically in the last 25 years. India has the distinction to have the largest diabetic population, only next to China in the world. At present there are more than 2 crore individuals with diabetes in India and this is estimated to increase to 5.7 crores by 2025 [1].

It is well known that type 2 diabetes is preceded by a long asymptomatic period where individuals deteriorate from normal glucose tolerance to impaired glucose tolerance and are later diagnosed with type 2 diabetes. This period approximates between 10 to 15 years differing in individual subjects. It is noted from epidemiological studies that impaired glucose tolerance (IGT) and impaired fasting glycaemia (IFG) are metabolic states with increased risk of future type 2 diabetes, of which at-least 30-50 percent go on to develop diabetes[2,3]. Recent data from the Diabetes prevention programme study in the US showed that these prediabetic states are also associated with increased incidence of microvascular complications[4]. There is now good evidence that lifestyle or pharmacological interventions at this stage are beneficial in preventing or delaying the onset of diabetes[5,6]. In this review we discuss the pathogenic mechanisms responsible for the change from normal glucose tolerance to pre-diabetes and type 2 diabetes.

Type 2 Diabetes clusters in families and studies in first-degree relatives of type 2 diabetic parents and in twins have provided strong evidence for the genetic basis of insulin resistance and β-cell dysfunction. At least 40- 50 % of siblings of subjects with type 2 diabetes can expect to develop the condition. The risk

of developing diabetes was estimated at 2 to 4 times in offspring's with one or two affected parents. Further evidence comes from a number of twin studies, where monozygotic twins who share identical genetic information showed that the concordance rate for type 2 diabetes was significantly increased at 58% compared with the expected background population[7-9]. Prevalence of type 2 diabetes varies greatly between ethnic populations and in different parts of the world. It remains a common question whether this increased risk in certain populations is due to common environmental or genetic determinants. The genetic influence is supported by the fact that type 2 diabetes has a higher prevalence in certain populations like Asian Indians, American Indians and Pacific islanders. The prevalence is even higher when there is limited foreign genetic mixture as shown in Pima Indians[8].

Thrifty genotype hypothesis

Neel et al postulated that humans are genetically programmed for the hunter- gatherer era and carry an evolutionary advantageous thrifty genotype which promotes increased lipid storage in times of plenty, which would then confer a survival advantage during famines and natural disasters[10]. This would explain the increased incidence of obesity and type 2 diabetes in Pima Indians, Australian Aborigines and Pacific Islanders who until recently have followed a traditional lifestyle. When these populations are exposed to a Western diet with excessive energy through simple carbohydrates and increased saturated fat intake accompanied by a reduction in physical activity, the favourable metabolic profile becomes a handicap leading to obesity and type 2 diabetes[10].

Thrifty phenotype hypothesis

Barker and Hales hypothesised that intrauterine malnutrition leads to low birth weight and permanent changes in structure and function in the foetus, which predispose these individuals to have a higher risk of diabetes in adult life. This has been postulated on the basis of epidemiological observations linking low birth weight to hypertension, obesity and diabetes. Due to the strong genetic nature of type 2 diabetes it could also be said that the surviving low birth weight babies are also an example of the thrifty genes[11]. Type 2 diabetes is caused by a combination of impaired insulin action, defective insulin secretion and inadequate suppression of hepatic glucose output (figure 1). During a meal, the normal response is to suppress hepatic glucose output (HGO) and to enhance glucose uptake in the liver and muscle[12]. This needs an appropriate insulin secretory response and adequate hepatic and muscle insulin sensitivity for glucose uptake. It is important to note that pre-diabetes forms a part of continuum between normal glucose tolerance and diabetes. And clearly most abnormalities like insulin resistance and defects in beta cell function which have been noted in the diabetic state have been identified in pre-diabetic individuals and even in glucose tolerant first degree relatives of subjects with type 2 diabetes. It is evident that these changes happen long before the development of diabetes[13].

Does insulin resistance or beta cell dysfunction play an important role?

Insulin resistance is present in at least 90% of individuals with type 2 diabetes and equally in individuals with IGT. But not all individuals with insulin resistance develop type 2 diabetes. As long as the beta-cells are able to augment their secretion of insulin sufficiently to offset the insulin resistance, glucose tolerance remains normal. In individuals with preponderance to type 2 diabetes, there is a limitation to this hypersecretion of insulin. The onset of type 2 diabetes is associated with no further deterioration in insulin sensitivity; rather insulin secretion declined and fails to compensate for prevailing insulin resistance[14]. Data from newly diagnosed type 2 diabetic subjects in the UKPDS study clearly showed that subjects had already lost 50% of their beta cell function when a clinical diagnosis of diabetes is made[15]. Hence in pre-diabetes, with time the beta-cells begin to fail and initially the postprandial plasma glucose levels and subsequently the fasting plasma glucose concentration begins to rise, leading to the onset of overt diabetes.

Muscle

Skeletal muscle is responsible for 80% of glucose disposal in peripheral tissues and hence plays an important part in regulating carbohydrate metabolism. Glucose uptake in muscle is activated by the binding of insulin to its glycoprotein receptor which is located in the plasma membrane. This insulin receptor has two alpha and two beta units and binding of insulin to the alpha units leads to phosphorylation of specific tyrosine residues in the beta subunit thereby resulting in activation of the receptor. This leads to activation of various pathways inside the cell leading to stimulation of glycogen synthesis, protein synthesis, lipid synthesis, mitogenesis and activation of the GLUT4. In type 2 diabetes the ability of insulin to stimulate glucose uptake in muscle, glycogen synthesis and glucose oxidation are impaired[16]. These defects have also been identified in individuals with IGT and glucose tolerant first degree relatives of type 2 diabetes[12]. In individuals with IGT as in type 2 diabetic individuals, the most proximal defect in the signalling pathway has been identified as the inability of insulin to stimulate tyrosine phosphorylation of its receptor. Defects in the activation of insulin receptor substrate-1 (IRS-1) and reduced ability to associate with the p85 subunit of phosphatidyl-inositol-3 (PI-3) kinase have been identified recently[17,18]. Other studies have noted decreased activation of PI-3 kinase and reduced GLUT4 translocation. Work on human skeletal muscle cultures from insulin resistant normal glucose tolerant first degree relatives of type 2 diabetes identified a defect in insulin mediated glycogen synthesis[19].

Liver

Type 2 diabetes is characterised by a raised fasting blood glucose which is associated with increased hepatic glucose production (HGP). In normal individuals, HGP is suppressed markedly even with small increments of insulin. In individuals with diabetes this sensitivity is lost in spite of hyperinsulinemia [20-22].
Hepatic glucose production is also regulated by factors

such as glucagon and FFA which stimulate HGP. In vitro studies have demonstrated that plasma FFA are potent stimulators of HGP and do so by increasing the activity of pyruvate carboxylase and phosphoenol pyruvate carboxykinase, the rate limiting enzymes for gluconeogenesis[23,24]. Reduced suppression of hepatic glucose production has also been found in subjects with IGT[20].

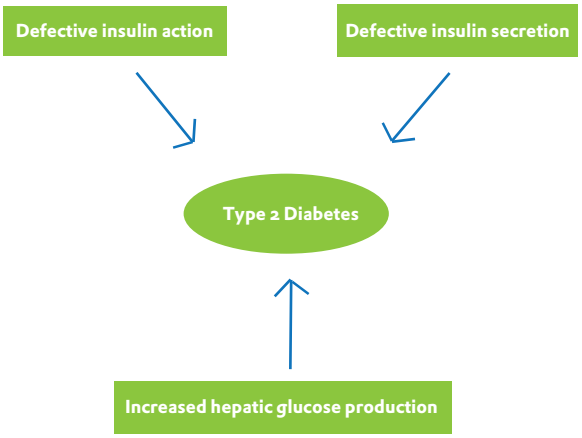

Fig1. Pathogenesis of Type 2 Diabetes

From the Triumvirate to the Ominous Octet

Recent evidence has accumulated to expand the conventional thinking of insulin resistance, reduced beta-cell function and increased hepatic glucose output as major factors for type 2 diabetes. New evidence in favour of the fat cell, incretin pathway, the alpha cells of islet of Langerhans, kidney and the brain as key regulators of glucose metabolism have become more evident in the last decade[25].

Fat Cell

Fat cells are resistant to insulin's antilipolytic effect, leading to day-long elevation in the plasma FFA concentration. Chronically increased plasma FFA levels stimulate gluconeogenesis, induce hepatic and muscle insulin resistance and impair insulin secretion. FFA also enhance the activity of glucose-6-phosphatase, the enzyme that ultimately controls the release of glucose by the liver[26]. Dysfunctional adipocytes produce excess amount of pro-inflammatory adipocytokines like IL-6, TNF - α, Leptin and Visfatin which induce insulin resistance and atherosclerosis. Also, they fail to secrete normal amounts of insulin-sensitizing adipocytokines such as adiponectin. Enlarged fat cells are insulin resistant and have diminished capacity to store fat. When adipocyte storage capacity is exceeded, lipid "overflows" into muscle, liver, and β-cells, causing muscle and hepatic insulin resistance and impaired insulin secretion. Lipid can also overflow into arterial vascular smooth cells, leading to the acceleration of atherosclerosis[27].

Incretins

Gut-derived hormones (Incretins) are secreted in response to oral ingestion of nutrients that potentiate insulin secretion and suppress glucagon secretion in a glucose-dependent fashion. Two predominant incretins are Glucagon-like peptide-1 (GLP-1) and Glucose-dependent insulinotropic peptide (GIP). GLP-1 is rapidly inactivated by dipeptidyl peptidase-4. Upon food ingestion, GLP-1 is secreted into the circulation from L cells of small intestine. GLP-1 increases glucose-dependent insulin secretion, reduce the rate of gastric emptying and decrease postprandial glucagon secretion. GLP-1 has an indirect benefit on beta-cell workload, since decreased glucagon secretion will produce decreased postprandial hepatic glucose output. It has effects on the central nervous system, resulting in increased satiety and a reduction of total food intake[28,29]. These actions, collectively called the "Incretin effect" is impaired in type 2 diabetes.

Glucagon

Glucagon secretion has been noted to be increased in type 2 diabetics and found to contribute to hyperglycemia mostly through glycogenolyis and gluconeogenesis. Increased glucagon levels in Type 2 diabetes leads to increased hepatic glucose output leading to elevated fasting blood glucose. Increased glucagon has been noted in postmenopausal women with IGT. Abnormal glucagon response in IGT is normalised by adequate insulinisation as in Type 1 diabetes. Glucose and insulin suppress glucagon secretion. Increased glucagon in the presence of the above proves inadequate suppression of alpha cell. Alpha cell insensitivity to insulin may be just a part of tissue insulin resistance leading to hyperglucagonemia. Alpha and beta cells may be regulated in parallel through autonomic nerves in the endocrine pancreas. Recent reports suggest an inverse relationship between plasma glucagon levels and insulin sensitivity. There is also evidence that the liver may be hypersensitive to the stimulatory effect of glucagon in hepatic gluconeogenesis[30].

Kidney

The most recent and unexpected member implicated in the pathogenesis of type 2 diabetes is the kidney. The kidney filters approximately around 162 grams of glucose every day. Ninety percent of the filtered glucose is reabsorbed by the high capacity SGLT2 transporter in the convoluted segment of the proximal tubule and the remaining 10% of the filtered glucose is reabsorbed by the SGLT1 transporter in the straight segment of the descending proximal tubule. The result is that no glucose appears in the urine. In animal models of both type 1 and type 2 diabetes, the maximal renal tubular reabsorptive capacity for glucose is increased. Thus, an adaptive response by the kidney to conserve glucose, which is essential to meet the energy demands of the body, especially the brain and other neural tissues, which have an obligate need for glucose, becomes maladaptive in the diabetic patient. Instead of dumping glucose in the urine to correct the hyperglycemia, the kidney chooses to hold on to the glucose. Even worse, the ability of the diabetic kidney to reabsorb glucose appears to be augmented by an absolute increase in the renal reabsorptive capacity for glucose. In summary, the development of medications

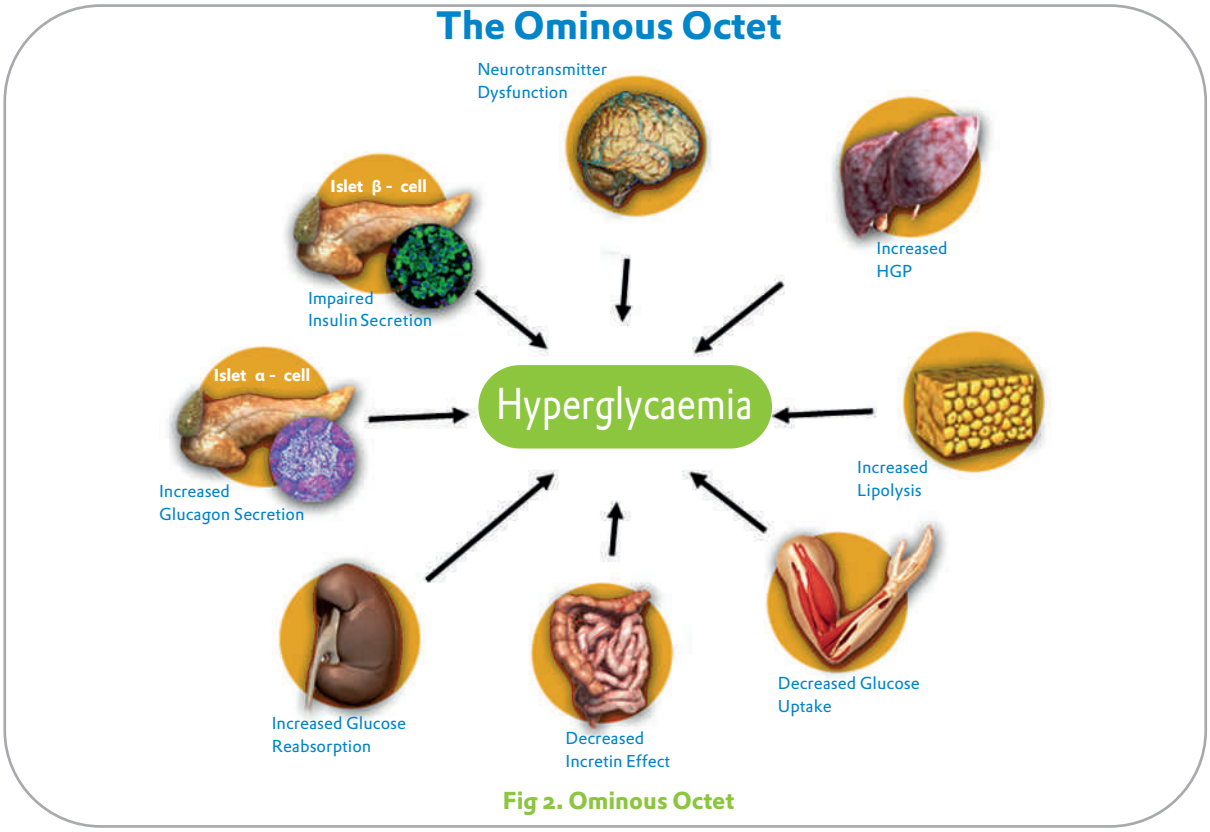

Fig 2. Ominous Octet

that inhibit renal proximal tubular glucose reabsorption provides a rational approach to the treatment of type 2 diabetes[31].

Brain

Last but not the least an important player in the pathogenesis of type 2 diabetes is the brain. It is widely accepted that the current pandemic of type 2 diabetes is related to the ever expanding problem of obesity in all populations. It is suggested that the peripheral insulin resistance which is prevalent in pre-diabetes and obesity may extend to the brain. The most important areas for regulation of appetite are the ventromedial and paraventricular nucleus of the hypothalamus. The magnitude of the inhibitory response following glucose ingestion is reduced in obese, insulin-resistant, normal glucose tolerant subjects, and there is a delay in the time taken to reach the maximum inhibitory response. It is also suggested that this could lead to increased HGP and reduced glucose uptake in the muscle[32].

Treatment of type 2 diabetes mellitus

Although several newer drugs targeting various patho-physiological aspects of type 2 diabetes mellitus are being introduced in the market, lifestyle intervention remains the cornerstone in the management of type 2 diabetes mellitus. The components of lifestyle intervention include medical nutrition therapy, exercise recommendations and comprehensive diabetes education. As majority of type 2 diabetics are obese, the goals of lifestyle intervention measures are:

- Achieving weight reduction- 5-7% of initial weight.
- Improving glycemic control.
- Improving insulin sensitivity.
- Cardiovascular fitness and
- Management of co-morbidities like dyslipidemia and hypertension.

Medical Nutrition Therapy (MNT)

Reduced calorie intake through reduction in carbohydrate (eg. avoiding sugar sweetened beverages) and fat intake (saturated fat <7% of total calories), carbohydrate counting and meal exchanges, optimal protein (0.8-1.0g/kg of body weight), dietary fiber (14gms/1000kcal) intake, consumption of alcohol and non-nutritive sweeteners within the acceptable daily intake levels and individualized meal planning are the key components of MNT[33].

Physical activity

People with diabetes should be advised to perform at least 150 min/week of moderate-intensity aerobic physical activity (50–70% of maximum heart rate), spread over at least 3 days per week with no more than 2 consecutive days without exercise. Regular exercise has been shown to improve blood glucose control, reduce cardiovascular risk factors, contribute to weight loss, and improve well-being. Furthermore, regular exercise may prevent type 2 diabetes in high-risk individuals [4-6]. Diabetic patients with multiple cardiovascular risk factors should be screened for coronary artery disease before initiating exercise training program.

Pharmacotherapy

The major group of drugs used in the management of type 2 diabetes mellitus include:

1. Insulin Secretogogues- Sulphonylyurea (Glibenclamide, Glipizide, Gliclazide, Glimeperide) & Meglitinides (Repaglinide & Nateglinide).

2. Insulin sensitizers- Metformin & Thiozolidinediones (Pioglitazone).

3. Incretin based therapies- GLP-1 Analogues (Exenatide and Liragutide) & DDP-4 inhibitors (Sitagliptin, Vildaglitin, Saxagliptin and Linagliptin).

4. Alpha Glucosidase inhibitors- Acarbose, Voglibose & Miglitol.

5. Bromocriptine.

6. Insulins- Human insulins & Insulin analogues.

The guidelines for using these drugs are laid down and periodically revised by major international organizations like American Diabetes Association (ADA), European Association for the study of Diabetes (EASD) and American Association of Clinical Endocrinologists (AACE). The goals of therapy are to maintain optimal levels of fasting, post-prandial plasma glucose levels and HbA1c (<6.5% as per AACE guidelines and <7% as per ADA guidelines). However, the choice of therapy should be individualized based on the age of the patient, duration of diabetes, presence of co-morbidities like obesity, nephropathy, coronary artery disease and most importantly risk of hypoglycaemia.

Metformin (unless contra-indicated or not tolerated) is the drug of choice for patients who have sub-optimal glycemic control after life style modification measures. As Metformin addresses the basic pathophysiology (Insulin resistance) of type 2 diabetes mellitus, helps to achieve glycemic control with negligible hypoglycemic risk, does not cause weight gain and reduces the cardiovascular risk in diabetics, it is still considered as the first choice even after several years of its introduction. Sulphonylurea or Incretin based therapies are considered as second line drugs if glycemic targets are not achieved even after adhering to lifestyle measures and use of Metformin. Because of the risk of hypoglycemia and weight gain, Sulphonylureas are slowly being replaced by Incretin-mimetics as second line agents.

The role of Incretins in the pathophysiology of type 2 diabetes has already been discussed. Consequently, GLP-1 analogues (which delivers supra-physiological doses of GLP-1 when injected subcutaneously) and oral DPP-4 (An enzyme which degrades endogenous GLP-1) inhibitors have been developed for the management of type 2 diabetes. These drugs are either weight neutral (DPP-IV inhibitors) or produce weight loss (GLP-1 analogues).

Their use is associated with lesser incidence of hypoglycemia than Sulphonylureas. However, the cost of the therapy and the unknown long term side-effects limit their use in many Indian patients with type 2 diabetes. Although oral gliptins such as sitagliptin, saxagliptin and vildagliptin have now established as market leaders, there remains an array of newer gliptins such as linagliptin and dutogliptin which are due to make a mark in the Indian market. Despite the limited success of the more potent injectable counterparts such as exenatide and liraglutide, there are also newer versions such as albiglutide and Taspoglutide in the final phases of drug research. A long-acting version of exenatide is also available in Europe.

Rosiglitazone, a drug belonging to the group of Thiazolidinediones, was withdrawn from market due to increased cardiovascular risk. Another drug in this group, Pioglitazone is still being used in the management of type 2 diabetes, though it produces weight gain, edema, anaemia and increased risk of fractures. There is evidence that the incidence of malignancies of the urinary bladder could be increased after use of pioglitazone and hence has to be used cautiously. Other drugs like Alpha-glucosidase inhibitors and Bromocriptine are mainly used as add- on therapies due to their less significant effect on HbA1c.

Properties	GLP-1 Analogues	DPP-4 inhibitors
Route of administration	Subcutaneous injection	Oral
Insulin secretion	Enhanced	Enhanced
Glucagon secretion	Suppressed	Suppressed
HbA,c reduction	-0.6% to -1.9%*	-0.5% to-0.8%*
Posprandial hyperglycemia	Reduced	Reduced
Body weight	Reduced	Neutral
Appetite	Suppressed	No effect
Gastric emptying	Delayed	No effect
Hypoglycemia	Low rate	Low rate
Gastro-intestinal effects	Nausea, Vomiting	No side effects
Cardiovascular risk factors	Decreases with weight loss	No consistent change

*-Average values obtained from several studies

Table 1. Comparison of GLP-1 analogues and DPP-4 inhibitors

Another class of agents which has shown promising results are the Sodium dependent glucose transport (SGLT2) inhibitors. They block the reabsorption of glucose by the kidney thereby promoting glycosuria in consequence improving blood glucose levels in patients with type 2 DM. Although the theoretical possibility of urinary tract infection remains, the real risk seems to be negligible in large clinical studies. Dapagliflozin has been approved in Europe and Canagliflozin is currently being evaluated by the FDA. However, the US FDA has not approved Dapagliflozin due to a numerical increase in breast and bladder cancer seen in the clinical studies. Protein tyrosine phosphatase 1B (PTP1B) inhibitors, Adenosine monophosphate-activated proteinkinase (AMPK) activators, Ghrelin receptor antagonists, Glucokinase acticvators are in phase 2 and 3 clinical studies and may be available as treatment for Type 2 Diabetes, Metabolic syndrome and Obesity.

Insulin therapy in type 2 diabetes is considered in situations like 1) failure to achieve target HbA1c even after combination drug therapy – progression of Type 2 diabetes 2) Emergency situations like Diabetic ketoacidosis, Hyperosmolar Hyperglycemic states, acute illnesses, peri-operative period and pregnancy.

Progression of Type 2 diabetes due to the loss of pancreatic beta-cell function irrespective of glycaemic control remains a significant disadvantage of conventional diabetic therapies. Established drugs for treating type 2 diabetes i.e. insulin, sulfonylureas, and glitazones also cause weight gain. Severe hypoglycaemia remains a serious risk with improving glycaemic control, especially with insulin and the sulfonylureas. There remains a need to develop new anti-diabetic drugs that lower blood glucose, while promoting weight loss and slow the progression of the disease. In the long-term; glucose lowering drugs should also have favourable effects on morbidity and mortality from microvascular and macrovascular complications of diabetes.

Summary

The pathophysiology of type 2 diabetes mellitus had been a subject of extensive research in the past decade. As a result, newer mechanisms were included to form an "Ominous octet" instead of the old "Triumvirate". Consequently, these newer targets provide scope for expansion of the therapeutic armamentarium of type 2 diabetes. Present and future research should be more focussed on the concept of "beta cell regeneration" and hence prevent progression of type 2 diabetes. This will be a major breakthrough in the management of type 2 diabetes and hopefully arrest the current diabetes pandemic.

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Review Article

Cardiovascular Disease In Diabetes – Prevention & Management

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Abstract

Among individuals with diabetes, cardiovascular disease (CVD) is the leading cause of morbidity and mortality. Adults with diabetes have a two- to fourfold higher risk of CVD compared with those without diabetes. Diabetes is also accompanied by a significantly increased prevalence of hypertension and dyslipidemia. The intent of this article is to clarify and reinforce the importance of identifying and treating a core set of risk factors (hypertension, dyslipidemia, obesity and tobacco use). Moreover, since recent evidence suggests that risk assessment and adherence to guidelines remain woefully suboptimal, we call for a renewed effort to prevent and treat these conditions.

Key Words : Cardiovascular disease, Diabetes, Prevention, Risk assessment, Risk management, Revascularisation.

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Introduction

Cardiovascular disease is the leading cause of morbidity and mortality in people with diabetes mellitus[1,2]. Aggressive control of hypertension and lowering cholesterol levels with statins reduce the risk of cardiovascular events, and there is conclusive evidence that improving glycaemic control significantly reduces the risk of developing diabetic microvascular complications (retinopathy, nephropathy, and neuropathy)[3,4,5]. But there is little evidence that specifically targeting glycaemic control can reduce the frequency of cardiovascular endpoints.

With the exception of glucose management, prevention of CVD follows the same general principles as for people without diabetes. A multifactorial approach to treatment and achieving low BP levels and low LDL and total cholesterol concentrations is particularly important, many of the treatment targets are tougher for patients with diabetes. The typical patient with type 2 diabetes has multiple cardiovascular risk factors, each of which should be treated in accordance with existing guidelines.

A high priority must be given to modification of the major risk factors for CVD in patients with diabetes. Increasing evidence indicates that controlling CVD risk factors will reduce onset of CVD and its complications in patients with diabetes. In the clinical management of patients with diabetes, attention must be given both to major risk factors (cigarette smoking, hypertension, elevated LDL cholesterol and diabetic dyslipidemia, and hyperglycemia) and to underlying risk factors (overweight/obesity, physical inactivity, and adverse nutrition)

Pathogenesis of Atherosclerosis in Diabetes

The pathogenesis of atherosclerosis in diabetes is complex and multifactorial. Five general areas of mechanism were defined. Metabolic factors, excessive oxidation/glucoxidation, endothelial dysfunction, inflammation, prothrombotic state. Overall, a better understanding of the pathophysiological mechanisms of atherosclerosis may provide a better understanding of the process in general.

Glucose control

The UKPDS evaluated the effect of improved metabolic control on the risk of developing CVD.[1,2] The study demonstrated a 16% risk reduction for myocardial infarction that was not statistically significantly (P 0.052) associated with the 0.9% difference in HbA1c that was obtained between the intensive and conventional treatment groups. In overweight patients treated with metformin, a significant reduction in risk of myocardial infarctions was seen(P , 0.01).

Three recent trails were conducted to see if cardiovascular events could be reduced further with lower target HbA1c levels.[3,4,5] In the ACCORD study, 10,000 patients with type 2 diabetes and either a history of CVD or additional cardiovascular risk factors were randomized to intensive therapy, with a target HbA1c,6.0% or standard glycaemic control target HbA1c 7.0–7.9%, The trial was stopped prematurely at 3.5 years due to a significantly increased total mortality in the intensive treatment group: 257 vs. 203 (p = 0.04) for deaths due to any cause and 135 vs. There were

significantly more cases of hypoglycaemia requiring assistance in the intensive group, who also experienced significantly more weight gain. The reason for the poorer outcome in the intensive group is not clear, but may be associated with hypoglycaemia.

The Action in Diabetes and Vascular Disease Trial (ADVANCE) randomized .11 000 patients with type 2 diabetes to either standard or intensive glucose control.[3] Intensive control significantly reduced the total number of major macrovascular events (death from cardiovascular causes, non-fatal myocardial infarction, nonfatal stroke) and major microvascular events (new or worsening nephropathy or retinopathy), but only the reduction in microvascular events was statistically significant. Weight gain and hypoglycaemia were less frequent than in the ACCORD study.

Recent meta-analysis examined trials of intensive vs. conventional glycaemic control,Showed a significant reduction in CHD and CVD events, but no reduction in cardiovascular mortality or total mortality.

Blood Pressure management

Epidemiological analyses and randomized clinical trials have demonstrated the impact of elevated blood pressure as a risk factor for both microvascular and macrovascular disease in diabetes. Blood pressure management is the most critical aspect of the care of the patient with diabetes.

The Hypertension Optimal Treatment trial[6] randomized patients with diastolic blood pressure of 100 to 115 mm Hg to diastolic blood pressure targets of ≤ 90, ≤85, and ≤80 mm Hg. It demonstrated a significant decline in the rate of major cardiovascular events with lower diastolic blood pressure targets. In the group randomized to a diastolic target of ≤80 mm Hg, the risk of major cardiovascular events was halved compared with the group with a target of ≤90 mm Hg.[6] For patients with diabetes, it generally is agreed that the appropriate diastolic blood pressure target is ≤ 80 mm Hg.

In a substudy of the UKPDS, patients with hypertension were randomized to intensive (mean BP 144/82 mmHg) or less intensive antihypertensive therapy.[7] There was a marked and significant 44% risk reduction for stroke and a non-significant 21% risk reduction for myocardial infarction associated with a 10 mmHg reduction in SBP and a 5 mmHg reduction in DBP.

In the ADVANCE BP study, lowering BP to a mean of 135/75 mmHg further reduced the risk of cardiovascular events and total mortality.[8]

In diabetic patients, antihypertensive treatment should be initiated when the BP is ≥140/80 mmHg. The SBP goal traditionally recommended in diabetes (i.e. ,130 mmHg) is based on epidemiological evidence, and not on evidence from randomized trials.

Regardless of the initial therapy, most patients will require multiple-drug therapy for hypertension in the setting of diabetes. Thiazide diuretics, β-blockers, ACE inhibitors, ARBs, and calcium channel blockers are beneficial in reducing CVD incidence in patients with diabetes. Current guidelines suggest that ACE inhibitors are the drugs of choice in the initial management of hypertension in people with diabetes or kidney disease.A low-dose thiazide diuretic generally should be one of the first 2 drugs used for management of hypertension in these patients.

Dyslipidaemia

In patients with type 2 diabetes mellitus, triglycerides are often elevated, HDL-C is generally decreased, and LDL-C may be elevated, borderline, or normal. LDL particles are small and dense, carrying less cholesterol per particle. Thus, the LDL-C concentration may be misleading: There will be more LDL particles for any cholesterol concentration if the LDL particles are small and dense. Additionally, these small, dense LDL particles may be more atherogenic than would be suspected by their concentration[9] .

Earlier and intensive prevention using lipid-lowering drugs irrespective of basal LDL cholesterol and aiming at lower lipid level goals, particularly in patients with type 2 diabetes, is needed. For patients with type 2 diabetes who have overt CVD or CKD and have one or more other CVD risk factors, the optimal level of LDL cholesterol should be 70 mg/dL.

However, it has to be stressed that in patients with type 2 diabetes, LDL cholesterol often remains within the normal range or is just moderately elevated, while one of the major CVD risk factors in these patients is diabetic dyslipidaemia characterized by hypertriglyceridaemia and low HDL cholesterol. Combination therapy of LDL-lowering drugs (eg, statins) with fibrates or niacin may be necessary to achieve lipid targets.

Antithrombotic therapy

The role of aspirin in primary prevention remains unproven. In the HOT study, 75 mg of aspirin further reduced the risk of major cardiovascular events in well-controlled hypertensive patients with diabetes, but non-fatal major bleeds were significantly more common among patients receiving aspirin.[6]

A recent meta-analysis of six RCTs found no statistically significant reduction in the risk of major cardiovascular events or all-cause mortality when aspirin was compared with placebo or no aspirin in people with diabetes and no pre-existing CVD.[10]

Microalbuminuria and multifactorial intervention

Microalbuminuria (urinary albumin excretion from 30 to 300 mg/ 24 h) predicts the development of overt diabetic nephropathy in patients with type 1 or type 2

diabetes, while the presence of overt proteinuria (300 mg/24 h) generally indicates established renal parenchymal damage. In both diabetic and non-diabetic hypertensive patients, microalbuminuria—even below the currently used threshold values—predicts cardiovascular events, and a continuous relationship between cardiovascular as well as noncardiovascular mortality and urinary protein/creatinine ratios has been reported in several studies.

An intensified multifactorial intervention including glucose management, statins,ACE inhibitors, other antihypertensive agents, aspirin, and lifestyle interventions (smoking cessation, increased physical activity, and diet) demonstrated a significant reduction in the incidence of microvascular complications after 4 years and a significant 53% risk reduction in macrovascular complications after 8 years[10].After a further 5 years of observational follow-up this was associated with a significant reduction in cardiovascular mortality[11]. Thus in high-risk patients polypharmacological multifactorial intervention is needed to obtain the maximum risk reduction.

Lifestyle Management

Lifestyle measures such as medical nutrition therapy and aerobic exercise have been demonstrated to modify lipids and reduce blood pressure and are integral to the management of glycemia and weight control[12,13] .Numerous epidemiological analyses suggest that nutrition and physical activity are predictors of age-specific mortality and cardiovascular event rates. To date, short-term studies of medical nutrition therapy,[12] physical activity, and comprehensive lifestyle approaches have been shown to improve the control of risk factors and intermediate markers of CVD risk.

Weight

Weight reduction in obese persons will reduce all of the CVD risk factors associated with type 2 diabetes mellitus and will improve hyperglycemia. Moderate weight loss (eg, 7% to 10% of body weight in 1 year) is often attainable, whereas efforts to achieve ideal body weight in short periods of time usually fail. Even if no weight reduction can be achieved, weight maintenance is certainly preferable to weight gain. Diets low in carbohydrate may be associated with greater weight loss in the short term but have not been demonstrated to result in greater weight loss after 1 year than diets with more balanced proportions of fats and carbohydrates.[14]

To improve glycemic control and reduce the risk of CVD at least 150 minutes of moderate-intensity aerobic physical activity per week or at least 90 minutes of vigorous aerobic exercise per week is recommended. Thus, patients with diabetes should be encouraged to perform 30 to 60 minutes of moderate-intensity aerobic activity such as brisk walking on most (preferably all) days of the week, supplemented by an increase in daily lifestyle activities (eg, walking breaks during the workday, gardening, and household work).

Medical Nutrition Therapy

To achieve reductions in LDL-C, saturated fats should be <7% of energy intake, dietary cholesterol intake should be <200 mg/d, and intake of trans-unsaturated fatty acids should be <1% of energy intake. Total energy intake should be adjusted to achieve body-weight goals.

Total dietary fat intake should be moderated (25% to 35% of total calories) and should consist mainly of monounsaturated or polyunsaturated fat. Ample intake of dietary fiber (≥14 g per 1000 calories consumed) may be of benefit.

In both normotensive and hypertensive individuals, a reduction in sodium intake may lower blood pressure. The goal should be to reduce sodium intake to 1200 to 2300 mg/d (50 to 100 mmol/d), equivalent to 3000 to 6000 mg/d of sodium chloride.

Tobacco Use Cessation

All patients with diabetes should be asked about tobacco use status at every visit.Every tobacco user should be advised to quit. The patient can be assisted by counseling and by developing a cessation plan.Follow-up, referral to special programs, or pharmacotherapy (including nicotine replacement and bupropion) should be incorporated as needed

Management of CAD in diabetes

Screening

Coronary artery disease (CAD) is the leading cause of morbidity and mortality in patients with diabetes. CAD is often asymptomatic in these patients, until the onset of myocardial infarction or sudden cardiac death. Consequently, proper screening and diagnosis of CAD is crucial for the prevention and early treatment of coronary events.

Although it remains controver¬sial to screen asymptomatic patients with diabetes, screening patients with a limited functional status is probably a reasonable approach for people at moderate to high risk of underlying CAD. An exercise TMT can be a safe and effective initial screening test in patients who can exercise and have a normal baseline ECG. Screening should also be con¬sidered in patients with an abnormal ECG tracing suggestive of ischemia or infarction. Coronary arteriography remains the gold standard for identifying obstructive lesions, though it is never used as an initial screening test.

The treatment goals for patients with coronary artery atherosclerosis are to relieve symptoms of CAD and to prevent future cardiac events, such as unstable angina, AMI, and death. The mainstays of pharmacologic therapy of angina include nitrates, beta-blockers, statins, calcium-channel blockers, and ranolazine.The prevention and treatment of atherosclerosis requires control of the known modifiable risk factors for this disease. This includes therapeutic lifestyle changes and

the medical treatment of hypertension, hyperlipidemia, and diabetes mellitus.Typically, patients with CAD are first seen after they present with a cardiac event.

In the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial, of 2, 248 patients with stable CAD randomized to optimal medical therapy plus percutaneous coronary intervention (PCI) vs. optimal medical therapy alone, 766 patients (34%) had diabetes mellitus, and 1,362 patients (61%) had the metabolic syndrome[15]. At 4.6-year median follow-up, the risk of death or myocardial in infarction in patients with diabetes mellitus and in patients with the metabolic syndrome was similar in patients with and without early PCI.

These data favor optimal medical therapy alone in patients with diabetes mellitus and stable CAD. However, if disabling angina pectoris despite optimal medical therapy occurs coronary revascularization is recomended.

Revascularization therapies for symptomatic or ischemia-producing atherosclerotic lesions include percutaneous approaches and open heart surgery. Long-term mortality is similar after CABG and PCI in most patient subgroups with multivessel coronary artery disease; therefore, the choice of treatment should depend on patient preferences for other outcomes. Exceptions to this are patients with diabetes and those age 65 years or older; CABG is a superior option in these subgroups, because of lower mortality[16].

Conclusion

Intensive management of hyperglycaemia in diabetes reduces the risk of microvascular complications and, to a lesser extent,that of cardiovascular disease.Intensive treatment of hypertension in diabetes reduces the risk of macrovascular and microvascular outcomes and multiple antihypertensive drugs are usually required to reach the target. Increased plasma cholesterol and LDL cholesterol are among the main risk factors for CVD. Hypertriglyceridaemia and low HDL cholesterol are independent CVD risk factors. Statin therapy has a beneficial effect on atherosclerotic CVD outcomes.Lifestyle modification is an important aspect in the management.

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Good, Bad and the Ugly!

Most health-conscious people are aware of the eternal conflict between the "good" cholesterol ((High Density Lipoprotein) and the "bad" cholesterol (Low Density Lipoprotein) for the human heart and if "bad" gains the upper hand, heart may suffer a fatal damage. But that is not the whole story, because we have left out "Mr. Ugly". In a study published in the Journal of the American College of Cardiology, the authors after having examined 73,000 persons, have concluded that it is the "ugly" cholesterol that is truly harmful. It increases the risk of ischaemic heart disease by three times. "Ugly" cholesterol is 'remnant-like particle cholesterol'. Its level in the blood is high when the level of triglyceride (normal fat) is high. The authors hope that pharmaceutical industry will respond by developing new drugs to keep "Mr. Ugly" in check. (Journal of the American College of Cardiology, 2012; DOI:10.1016/j.jacc.2012.08.1026)

- Dr. K. Ramesh Rao

Review Article

Eye Manifestations of Diabetes Mellitus

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Introduction

Diabetes Mellitus (DM) was first described about 3500 years ago and given its name about 2200 years ago by Demetrios of Apamaia. The word "Diabetes" derives from the Greek "Diabeinein" or "siphon", a word that captures its association with excess urination. Although DM has been primarily regarded as a disorder of glucose metabolism and homeostasis, it has more recently been viewed as a constellation of metabolic disturbances, including abnormalities of carbohydrate metabolism, adipose storage, lipid metabolism, and protein biochemistry. Commonly characterized as a disease of impaired skeletal muscle glucose uptake, DM adversely affects hepatic, muscle, adipose and vascular function. It is this last effect that represents the greatest mortality and morbidity hazard to this subset of population.

Ocular Manifestations

DM affects all the parts of the eye from the lids to the retina and the cranial nerves. The part of the eye from the cornea to the posterior capsule of the lens forms the anterior segment of the eye and the structures behind the posterior capsule of the lens to the Optic nerve head and the retina forms the posterior segment of the eye.

Anterior segment manifestations

Lids and the adnexa

Hordeolum externum commonly called the stye is an acute suppurative inflammation of the eye lash follicle and its associated zeis glands. (Fig.1)

Fig 1. Hordeolum Externum

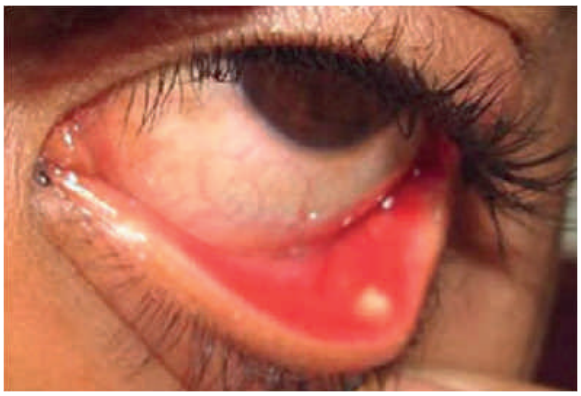

Fig 2. Hordeolum Internum

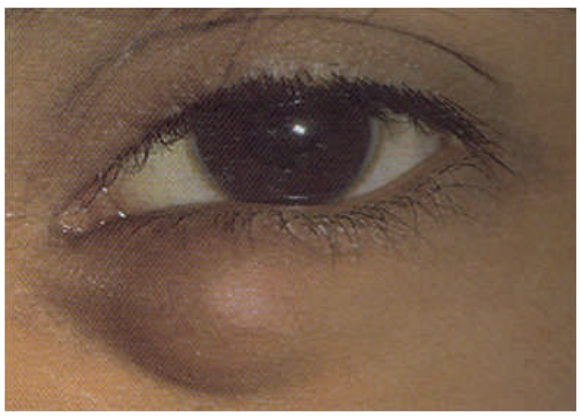

Fig 3. Chalazion

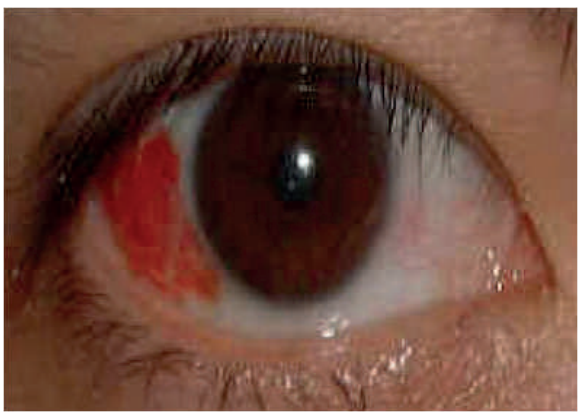

Fig 4. Sub conjunctival haemorrhage

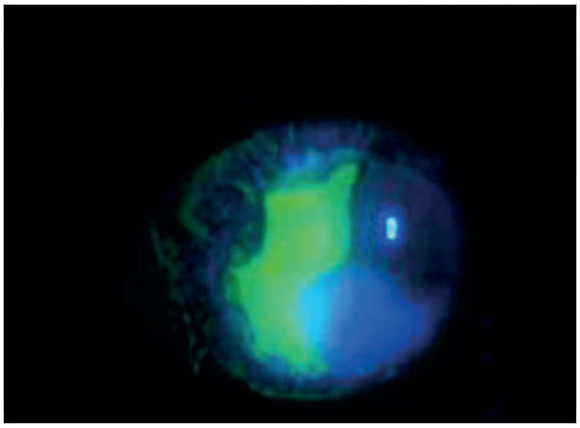

Fig 5. Fluorecsein staining of the corneal epithelial defect

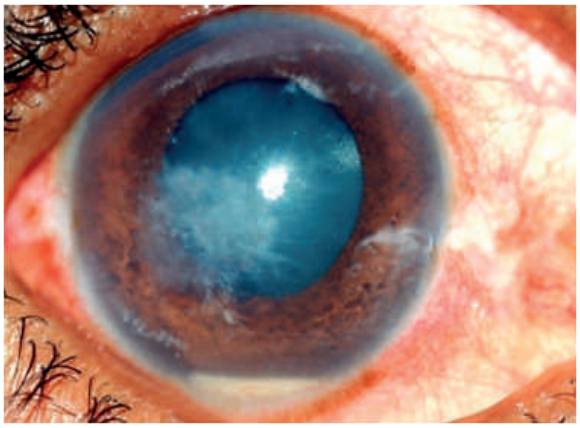

Fig 6. Fungal keratitis with hypopyon

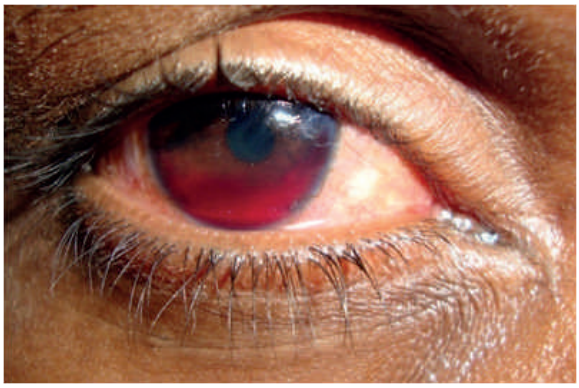

Fig 7. Hyphaema (Blood in the anterior chamber)

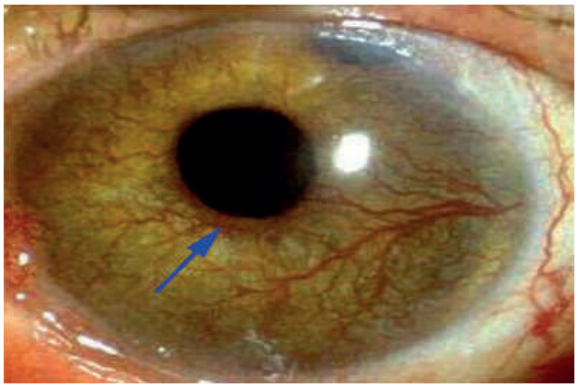

Fig 8. Ectropion uveae and rubeosis iridis

Hordeolum internum is an acute suppurative inflammation of the meibomian glands. (Fig.2)

Treatment of hordeolum externum and internum: Topical antibiotics, hot compresses, analgesics and if needed systemic antibiotics.

Chalazion is a chronic granulomatous inflammation of the meibomian glands. (Fig.3)

Treatment: Incision and curettage.

Conjunctiva

Recurrent sub conjunctival haemorrhages (SCH) and dry eye or xerosis of the conjunctiva. (Fig.4)

Treatment: Control of DM, vitamin-c supplements and reassurance.

Cornea

The cornea shows a decreased nerve fiber density and nerve conductivity causing decreased corneal sensation. Poor adherence of the epithelial basement membrane to the underlying stroma due to decreased number of hemidesmosomes leads the diabetics to develop recurrent corneal erosions even to trivial trauma and predispose them to bacterial and fungal keratitis and neurotrophic non healing corneal ulcers (Fig 5,6). In the early stages of uncontrolled or fluctuating levels of blood glucose in diabetics, cornea can become thick due to corneal edema causing blurred vision and later due to recurrent erosions they might become thin with persistent epithelial defects. So in young diabetics the role of refractive surgeries like LASIK (Laser Assisted In-Situ Keratomileusis) or PRK (Photorefractive Keratectomy) to correct refractive error becomes difficult and is associated with higher rates of complications. Same holds good for the use of contact lens in these individuals. They also have altered endothelial cell morphology so any intra ocular surgery like cataract surgery can cause corneal edema which might take days to resolve.

Treatment: Infective keratitis is appropriately treated with anti microbials and cycloplegics. Lubricant eye drops for dry eyes, corneal epithelial defects and recurrent erosions.

Anterior Chamber And The Angle

Many studies suggest a direct correlation between diabetes and Primary open angle glaucoma (POAG). Neovascular glaucoma (NVG) develops in patients having proliferative diabetic retinopathy (PDR) and advanced diabetic eye disease due to the development of neovascular membrane at the angle of the anterior chamber. These patients might sometime present with hyphaema. (Fig.7)

Treatment: Control of intra ocular pressure (IOP) with anti glaucoma medications. If not controlled filtering surgery with or without shunt and Mitomycin-C. If the eye is already blind diode cyclo-photocoagulation can be helpful to control the IOP.

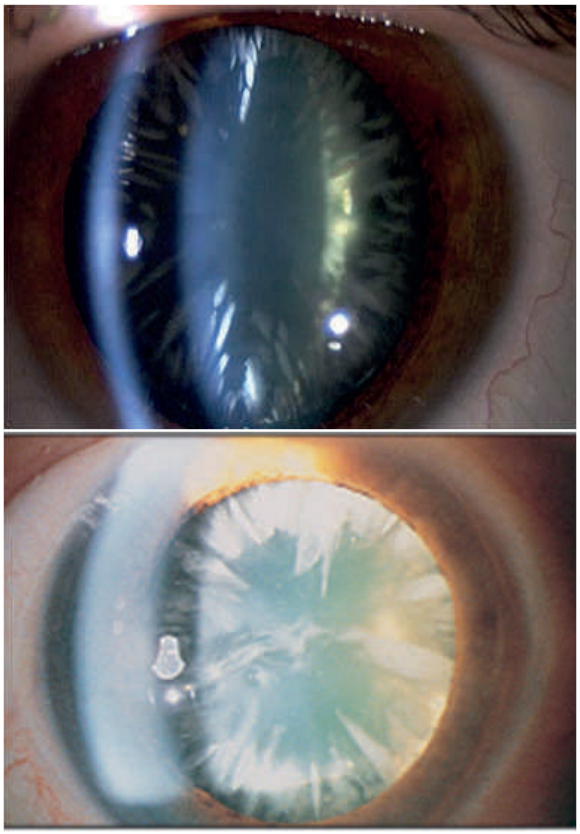

Fig 9. True diabetic cataract also called as snow flake cortical cataract.

Iris

The development of new vessels at the iris can be seen in patients with PDR. These are called as rubeosis iridis. (Fig.8)These patients also have a typical appearance of the iris at the papillary margin called as ectropion uveae.

Treatment: Treat the underlying PDR with Laser pan retinal photocoagulation if the media is clear or retinal cryopexy if the media is hazy to reduce the release of vascular endothelial growth factors (VEGF) which causes rubeosis and NVG

Pupil

Diabetics generally have a smaller pupil and show latency to dilatation with instillation of mydriatics during examination.

Lens

Transient fluctuating myopia occurs due to hyperglycemia induced change in the refractive index of the lens due to osmosis. Diabetics are at risk of developing cataract earlier compared to non diabetics and it depends on the glycemic control and the duration of the DM. The most common type is the cortical cataract and the posterior sub capsular cataract. (Fig.9)

Treatment: If visually significant, cataract surgery with intra ocular lens implantation is recommended.

Posterior Segment Manifestations

Vitreous

Asteroid hyalosis (Benson disease) is commonly seen in DM patients but not proven. These are calcium pyrophosphate globules collected within the vitreous gel.

Treatment: Generally visually insignificant. If it affects vision a optical vitrectomy is done.

Vitreous haemorrhage is commonly associated with proliferative diabetic retinopathy.

Retina

The prevalence of Diabetic retinopathy (DR) is probably up to 40%. It is more common in type 1 DM than in type 2 DM and sight threatening disease is seen in up to 10%

Risk Factors

1. Duration of DM is the most important risk factor.
2. Poor control of DM.
3. Pregnancy is associated with rapid progression of DR.
4. Hypertension.
5. Nephropathy.
6. Hyperlipidemia.
7. Other risk factors are obesity, smoking, complicated cataract surgery and anaemia.

Pathogenesis Of Diabetic Retinopathy[1]

DR is predominantly a microangiopathy in which small blood vessels are vulnerable to damage from hyperglycemia. The general pathophysiology described earlier is applicable to retina and retinal vasculature damage as well. Along with this there is capillaropathy and neovascularization. Capillaropathy is characterized by death of pericytes, thickening of capillary basement membrane, loss of vascular smooth muscle cells, and proliferation of endothelial cells. Neovascularization is caused by capillary non perfusion which leads to retinal hypoxia and stimulation of angiogenic factors like VEGF.

Classification of DR

Early treatment diabetic retinopathy study (ETDRS)/ the Modified Airlie House classification[10]

1. Non proliferative diabetic retinopathy (NPDR)

I. No DR

II. Mild NPDR

Retinal microaneurysm/retinal haemorrhage with hard or soft exudates in one quadrant of retina.

III. Moderate NPDR

Retinal haemorrhage/microaneurysm with hard or soft exudates in 1-3 quadrants of retina.

IV. Severe NPDR (Fig. 10,11)

The 4-2-1 rule; one or more of :

a. Severe haemorrhages in all 4 quadrants of retina

b. Venous beading in 2 or more quadrants

c. Moderate Intraretinal microvascular abnormalities (IRMA) in 1 or more quadrant

V. Very Severe NPDR
2 or more of the criteria for severe NPDR

2. Proliferative diabetic retinopathy

I. Early PDR

New vessel on the disc (NVD) or new vessel elsewhere (NVE) but in sufficient to meet the high risk criteria

II. High Risk PDR

a. NVD about 1/3 of the disc area

b. Any NVD with vitreous or pre retinal haemorrhage

c. NVE greater than ½ disc area with vitreous or pre retinal haemorrhage

III. Advanced Diabetic Eye Disease

a. Pre retinal or vitreous haemorrhage

b. Tractional retinal detachment (TRD) (Fig.12)

c. Rubeosis iridis

3. Diabetic maculopathy

I. Focal maculopathy

Well circumscribed retinal thickening associated with complete or incomplete rings of exudates

II. Diffuse Maculopathy
Diffuse retinal thickening with exudates

III. Ischemic Maculopathy

Macula may look normal with variable signs with decreased vision, confirmed with fundus fluorescein angigraphy

IV. Clinically Significant Macular Oedema (CSME/CSMO)

a. Retinal thickening within 500 microns of the center of the macula.

b. Exudates within 500 microns of the center of the macula, if associated with retinal thickening which may be outside the 500 microns

c. Retinal thickening one disc area (1500 microns) or larger, any part of which is within one disc diameter of the center of the macula.

Management of DR

Investigations

Regular follow up a DM patient with fasting and post prandial blood glucose levels and others like HbA1c, Hb, serum electrolytes and calcium, fasting lipid profile, serum blood urea nitrogen and creatinine on a periodical basis.

FFA is indicated to rule out PDR and for follow up after treatment for both PDR and maculopathy. Optical Coherence Tomography (OCT) helps in the follow up of patients with maculopathy before and after treatment as it is non invasive.

Treatment

Medical treatment[8]

NPDR just needs adequate glycemic control with control of other co morbid conditions like hypertension and dyslipidemia.

PDR needs pan retinal laser photocoagulation[7] (PRP) so as to convert a hypoxic retina into an anoxic retina in order to reduce the stimulus for the production of the angiogenic growth factors.

It can also be combined with intra vitreal injection of Bevacizumab[5,6] (Avastin), Ranibizumab (Lucentis) or Pegaptanib sodium (Macugen) which are the available anti-VEGF at present.

Maculopathy is treated with Focal or Grid Laser photo-coagulation with or without additional use of intra vitreal steroids like Dexamethasone (Posurdex), Triamcinolone[4] (Tricort) or anti- VEGF injections.

Surgical Treatment

Advanced diabetic eye diseases and patients with PDR/Maculopathy following ineffective medical management needs Pars plana vitrectomy[9], endo laser photocoagulation and retinal re-attachment surgeries. (Fig. 14,15)

Follow Up

The most important part of treatment in DR is the follow up which is very crucial for the preservation of useful visual acuity in these patients.

Mild NPDR	Every year
Moderate NPDR	Every year
Severe NPDR	Every 6 months
Very severe NPDR	Every 4 months
PDR & advanced eye diseases	Every 2 months

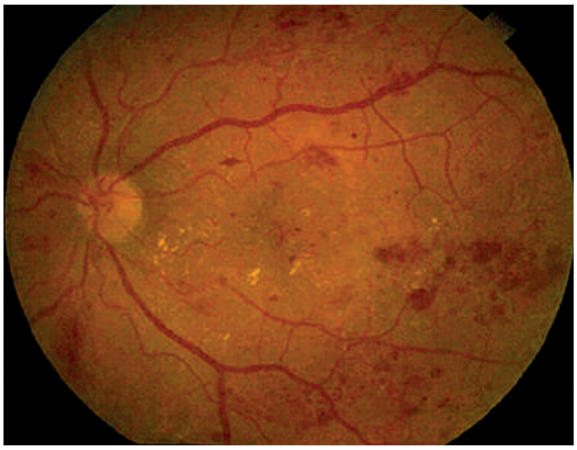

Fig 10. Severe NPDR

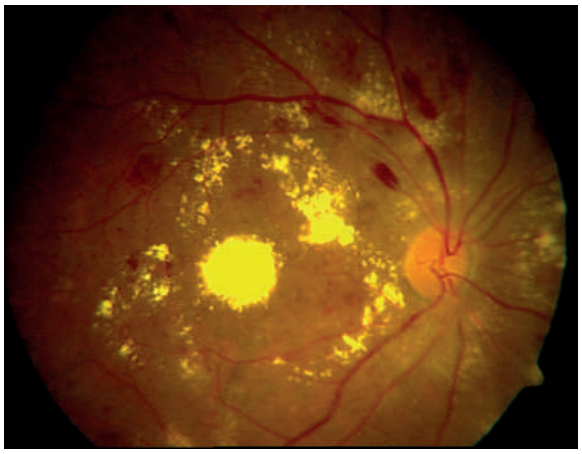

Fig 11. Severe NPDR with CSME

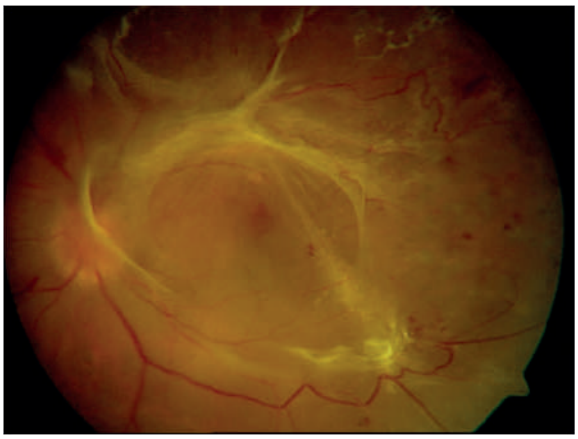

Fig 12. Advanced diabetic eye disease with TRD

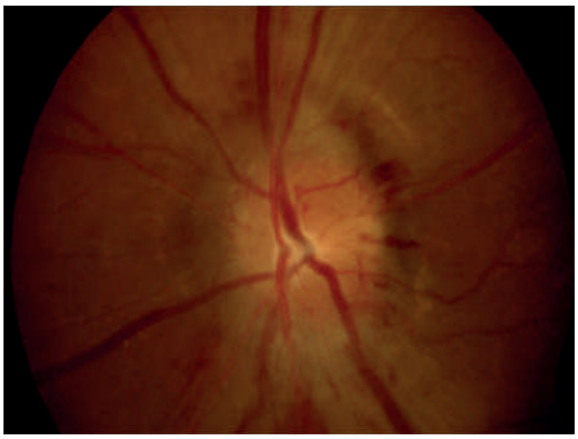

Fig 13. Diabetic papillopathy

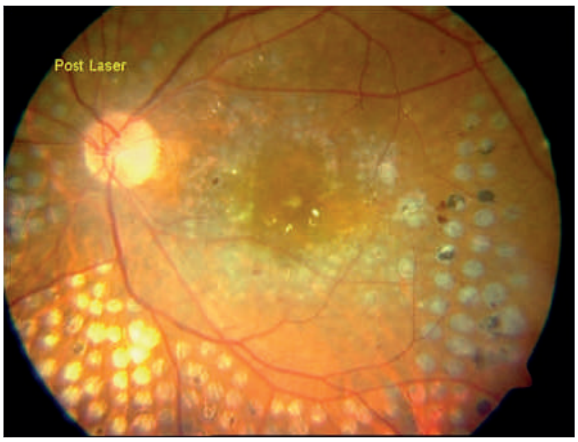

Fig 14. Post PRP Laser PHC

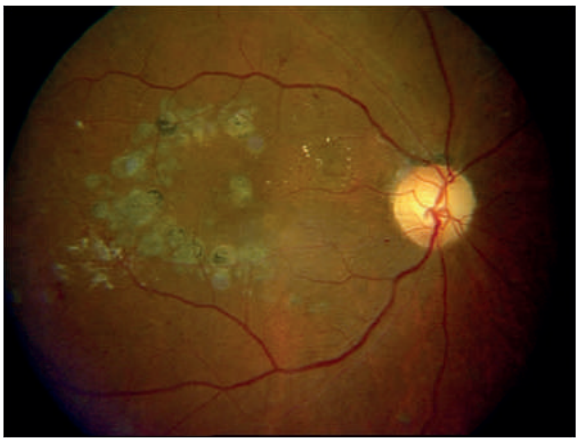

Fig 15. Post Focal Laser PHC for maculopathy

Neuro-Ophthalmic Manifestations Of DM

Some of the common neuro ophthalmological conditions seen associated with uncontrolled DM are

1. Non arteritic type of anterior ischemic optic neuropathy (NAION).
2. Diabetic papillopathy.
3. Cranial nerve palsies (Oculomotor and Abducens) and ophthalmoplegia.
4. Bilateral light near dissociation.
5. Orbital apex and superior orbital syndromes.

Conclusion

Creation of awareness for a prompt follow up of all patients with DM and other systemic diseases which affects the eyes and the vision is absolutely essential to prevent these patients ending up with PDR from the time a diagnosis of DM is made by the physician to avoid blindness and other ocular morbidities.

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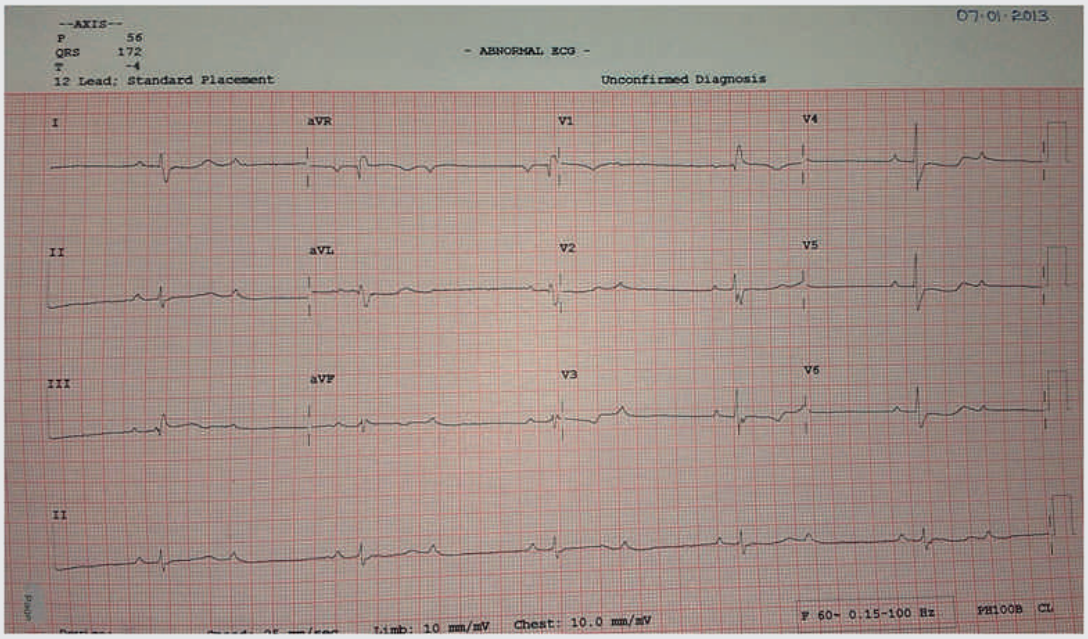
Diagnose the Condition

80 year old male, known case of type 2 diabetes mellitus with chronic renal failure admitted with history of occasional giddiness. ECG taken in the ICU.



Answer in page no: 176

- Dr. M.Chokkalingam, Consultant Cardiologist, CSSH.

Review Article

Paediatric Diabetes

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Abstract

Childhood onset diabetes is encountered more commonly than before. Previously, the main form of diabetes seen in young children was type 1 diabetes characterized by life threatening ketoacidosis without insulin treatment. However, with the alarming rise in childhood obesity worldwide, type 2 diabetes is increasingly seen in children. With advancement in molecular and genetic basis of diseases, other subtypes of diabetes in children which are monogenic in etiology like Maturity Onset Diabetes in Young (MODY) and neonatal diabetes due to sulphonyl receptor mutation responding to oral drugs are also added to the list of different varieties of diabetes seen in children. A brief review of diagnosis and approach to diabetes in young with special focus on various aspects of management of type 1 diabetes is discussed in this article.

Key Words : Diabetes in young, Childhood diabetes, Paediatric diabetes, Insulin therapy

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Type 1 Diabetes mellitus

Type 1 Diabetes mellitus (T1DM) is a condition characterized by beta cell destruction resulting in absolute insulinopenia predisposing the affected individuals to ketosis even in basal conditions. Though it can occur at any age, the onset is usually in younger children and hence the previous name juvenile onset diabetes. Since insulin is required for survival it is also aptly called insulin dependent diabetes mellitus (IDDM) though this name is not used anymore.

Pathogenesis

The basic pathophysiology is an immune mediated inflammatory destruction of pancreatic beta cells in a genetically susceptible individual.

Genetics

Clinical studies have shown a greater concordance rate of Type 1 DM among monozygotic than dizygotic twins. Also, the risk of developing T1DM is more among first degree relatives of a proband (5%) compared to overall risk of 0.2 -0.3% among general population. Offspring studies show that the risk is ~3% if the mother has the disease versus 6% if father is affected. Several genetic loci have been identified to have possible role in pathogenesis of T1DM, the leading loci are IDDM1 and IDDM2 on chromosome 6 and 11 respectively.[1]

HLA (Human Leucocyte Antigen) system complex

From population studies, there is a clear association between certain HLA alleles and T1DM, especially HLA DR, DQ and DP loci. The different HLA alleles and their strength of association with T1DM are shown in Table 1.

Table 1: Diabetes risk stratified based on HLA haplotypes

Risk	DRB1	DQA1	DQB1
Low (protective)	1101,1501,0701,1401	0501,0102,0201,0101	0301,0602,0303,0503
Moderate	0401,0403,0101,1601	0301,0101,0102	0301,0303,0501,0502
High	0401,0405,0402,0301,0801	0301,0501,0401	0302,0201,0402

Modified from teaching slides www.barbaradaviscenter.org

Environmental triggers

Discordance in the occurrence of T1DM among identical twins has been a favourable point for reasonable role of environmental triggers in the pathogenesis. From population observations in countries with higher incidence of T1DM there has been a suggestion of possible link between early initiation of cow's milk and T1DM. Possible mechanisms include molecular mimicry like effect between bovine serum albumin and beta cell antigens. Vitamin D deficiency has been associated with occurrence of T1DM mainly from epidemiological observations. Few studies of vitamin D supplementation in early infancy have shown little but promising results in reducing the incidence of T1DM.

Viral infections

Few cases of isolation of Coxsakie B virus from the deceased pancreatic islets and T1DM occurring in patients with congenital rubella link viruses in the pathophysiology. However, exact mechanisms have not been completely elucidated.

Chemical toxins

Nitrosourea compounds, alloxan, streptozocin and pentamidine have been linked with T1DM in some studies, however, only in genetically susceptible individuals.

Immunologic factors

Literature is replete with evidence for immunological mediation of beta cell destruction in T1DM. The immune processes involved in isolated T1DM are significantly different from the beta cell damage process that occurs in T1DM as a part of polyendocrinopathy syndrome. It is generally accepted that the immune destruction is "autoimmune" in origin. However, this too occurs mainly in genetically susceptible individual with possible environmental triggers.

Insulitis

Pathologically, mononuclear infiltration of pancreatic cells is observed near the clinical onset of T1DM. This is similar to the lymphocytic infiltration seen in other autoimmune endocrinopathies as in thyroid. Predominant destruction occurs due to activation of cell mediated immune process – NK cells, lymphocytes and macrophages are mainly involved.

Circulating antibodies

Antibodies to varieties of islet antigens are detected at diagnosis or even prior to onset of T1DM. They may serve as markers of immune damage to beta cells. Earliest antibody to appear is usually anti-insulin antibody and it may help predict rapidity in progression to overt diabetes. Glutamic Acid Decarboxylase (GAD 65) antibody and islet cell antibody are usually present in adult/adolescence onset T1DM. Also, more the number of antibodies present in an individual the risk of progression to T1DM is increased. The sensitivity of various clinically relevant autoantibodies are given in Table 2.Clinically these antibodies especially GAD and ICA are used to confirm underlying autoimmune process and may be helpful in predicting T1DM in the first degree relatives of probands. Immunological intervention early in the course of immune destruction may help abort the damage too. Few interventional studies especially with immunosuppressants like azathioprine or anti CD3 monoclonal antibodies have shown only modest albeit reasonable alteration in the course of the onset of disease.[2] T1DM may also occur in patients who have not been demonstrated to have autoantibodies called Type 1B by ADA classification.

Table 2: Autoantigens and sensitivity in predicting development of Type 1 Diabetes mellitus

Autoantigen	Sensitivity
Insulin	49-92%
GAD (Glutamic acid Decarboxylase)	65-75%
ZnT8 (Zinc transporter 8)	65-75%
ICA512/IA-2 (Islet tyrosine phosphatase)	74%
IA-2β/Phogrin	61%
Carboxypeptidase H	10%

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Presentation and Diagnosis

Usually typical osmotic symptoms like polyuria, polydipsia and weight loss, fatigue and weakness are the major manifestations of severe hyperglycemia. Significant number of children who are not diagnosed in this phase would end up with life threatening ketoacidosis and may land up in the emergency department with altered sensorium or even coma. The differentiation from type 2 diabetes and other varieties of diabetes in children is not always easy but certain pointers may help. Type 2 DM invariably occurs in an obese child with significant family history of adults with Type 2 DM and signs of insulin resistance (as discussed).

Laboratory evaluation

Classic presentation with osmotic symptoms like polyuria, polydipsia and weight loss with a casual

plasma glucose more than 200mg/dl would suffice to diagnose DM and presence of ketoacidosis strongly suggests T1DM. In other early and milder presentations a fasting and 2hr post glucose challenge test may be required. Other tests which are useful include glycosylated haemoglobin, C-peptide levels (in certain ambiguous situations). Circulating antibodies especially anti-islet cell, GAD 65 and anti-insulin antibodies, if significantly elevated, confirm autoimmunity. In addition, screening for other autoimmune disorders especially thyroid, adrenal and parathyroid dysfunction and celiac disease may be required as T1DM may be a part of polyglandular syndrome. Genetic testing is useful in diagnosing monogenic forms of diabetes like MODY (maturity onset diabetes in young) and are also very helpful in rare neonatal forms of diabetes associated with potassium channel or sulphonylurea receptor (SUR) abnormalities where the diabetes can be managed with oral sulphonylureas instead of insulin.[3]

Management

The main goals of management of T1DM are

- Achievement of near normal blood glucose levels as much as possible
- Avoidance of severe hypoglycaemia
- Ensure normal growth and puberty
- Prevent long-term complications of diabetes

A multidisciplinary team is required to manage these children effectively and should usually include a physician or paediatrician with special interest in diabetes, nutritionist and other specialists as the need may arise.[3,4]

Diet

Principles of diet in children with diabetes should be tailored to the patient's lifestyle and where possible should avoid drastic changes. Children should be encouraged to eat regular meals containing complex carbohydrates, to reduce refined sugar intake and to increase dietary fibre content. No particular food should be considered forbidden as this may lead to disturbed attitudes to food. Furthermore, to deprive children of some foods such as sweets which their friends consume may be psychologically damaging. Dietary principles may be improved only if the whole family can make similar modifications. Family should also be educated about the dietary treatment of the child experiencing hypoglycaemia or intercurrent illness and dietary management during parties and holidays. Timing of meals and snacks need to be discussed based on the insulin regime. For example, children receiving twice daily injections of premixed (regular + NPH) usually require a snack in between meals to avoid hypoglycaemia. On the other hand, patients on ultrashort acting analogues based basal bolus regime may not require a snack.[2,3]

Dietary composition

It is recommended that approximately 50% of dietary energy intake should be derived from carbohydrates, 35% from fat (mainly mono- and polyunsaturated fats), and 15% from proteins. Basically the approach is to allow the child to choose from certain number of carbohydrate containing foods ('portions') from a list of such foods, at each meal and snack time based on "healthy eating" principles and to involve the whole family. Carbohydrate exchange principles are also taught to the family. Recently, stress is on carbohydrate counting which may be easily done in the developed world.

Exercise

Children should be encouraged to involve in consistent daily physical activity.Supervisory personnel at school or at a park must be made aware of the presence of a child with diabetes and be provided with a source of quick acting carbohydrate to manage hypoglycaemia should it occur. Short burst activity would usually require extra carbohydrate intake just before or just after the exercise to accommodate for the increased demand for calories. However prolonged aerobic activity may result in delayed hypoglycaemia due to accentuation of insulin effect several hours afterward. In the latter case, it is preferable to reduce the insulin dose prior to the planned prolonged physical activity and to eat a snack after the exercise.

Insulin treatment

Insulin is lifesaving in T1DM and proper knowledge about various aspects of insulin therapy will go a long way in the long term management of these children. Insulin preparations available in India are shown in Table 3. A number of insulin regimes are available and one need to be aware that it should be flexible and family's needs and wishes also be considered. In resource poor setting like ours, financial background may also need to be kept in mind in selecting the right insulin. In general, the insulin analogues are 2-3 times costlier than conventional insulins.

Following diagnosis, most children would require around 0.5 units of insulin/kg body weight. There is some evidence that early aggressive insulin therapy may "rest" the damaged beta cells and help "induce" remission ("honeymoon") period of early T1DM when the child may go off insulin for some period (even upto 2 years occasionally). Pre-school children (<4yrs) may be very sensitive to rapid acting insulins and possible regimens in this age group may include once or twice daily isophane (NPH) insulin or the long acting analogues (glargine or detemir). With technological advancement in the pen devices for insulin delivery even 0.5 units may be given currently and is very useful especially in infants. In many older children, use of twice daily injections with a mixture of rapid/short acting and intermediate/long acting commonly in a ratio of 30:70 or 25:75 with two thirds of the daily requirement being given at breakfast time helps achieve reasonable glycemic control. This is especially

useful in the first few years of diagnosis or following "honeymoon" period.

In older children and adolescents especially for appropriately motivated children and families use of a basal – bolus regime may be the most appropriate. The latter comprises of a regular insulin or rapid acting analogue every time before meals and NPH or long acting analogue prior to bedtime. The long acting analogues like glargine and detemir which do not have significant peak help avoid nocturnal hypoglycemia. This regime is very flexible and can be adjusted based on the type and quantity of food taken and in a younger child who may eat erratically, the rapid acting analogue with very quick onset of action may be administered immediately after food intake. Children and/or their parents need to be educated to alter the dose of rapid acting insulin in line with the planned dietary intake and any anticipated exercise. Children initially treated in the hospital are less active than those treated at home and most of them will experience a fall in their glucose following discharge.[1,2,5,6.]

Sick day management

Any illness like infection can cause alteration in the blood glucose levels in a diabetic child. Rise in blood glucose levels can occur due to high level of stress hormones promoting gluconeogenesis and insulin resistance. Inadequate insulin levels can cause ketone body formation. If the child has poor oral intake, diarrhoea and vomiting, there is a risk of hypoglycemia. To avoid precipitation of DKA and hypoglycemia, certain rules have to be followed during sick day. The sick day rules include:

- Never stop insulin.
- Frequent blood glucose monitoring i.e every 4-6 hours.
- Check for urine ketones or blood ketones if Home Monitoring of Blood Glucose (HMBG) is high.
- Insulin dose to be increased or decreased based on HMBG.
- Maintenance of adequate hydration.
- Treatment of inter-current illness.

Table 3: Insulin preparations currently available in India and their pharmacokinetics

Type	**Insulin**	**Onset of action**	**Peak**	**Duration of action in hours**
Rapid acting (analogues)	Lispro	5-15min	30-90min	3-5
	Aspart	5-15min	30-90min	3-5
	Glulisine	5-15min	30-90min	3-5
Short acting	Regular insulin	30-60min	2-3h	5-8
Intermediate-acting	Isophane insulin (NPH)	2-4h	4-10h	10-16
Long-acting	Glargine	2-4h	No peak	20-24
	Detemir	2-4h	No peak	16-20
	Degludec **(yet to be introduced in Indian market)**	2-4 hrs	No peak	24 – 48
Premixed	70%NPH+30% Regular	30-60min	Dual	10-16
	50% NPH+50% Regular	30-60min	Dual	10-16
	70%NPA+30%Aspart	5-15min	Dual	10-16
	75%NPL+25%Lispro	5-15min	Dual	10-16
	50%NPL+50%Lispro	5-15min	Dual	10-16

- Recognise the "warning signs" and seek specialist advice if necessary- some of the warning signs include 1) recurrent vomiting, poor oral intake & dehydration 2) Persistent hyperglycemia or hypoglycemia despite insulin dose adjustment 3) Heavy ketonuria or ketonemia 4) Child is exhausted, confused, hyperventilating, dehydrated or having severe abdominal pain.[7]

Monitoring

Glycosylated Hemoglobin (HbA1c), which reflects average glycemic control in the previous 2-3 months helps in assessment of intermediate to long-term control of diabetes. However, day to day adjustment of insulin dosage and modification of dietary pattern can be made only with frequent monitoring of blood glucose. This is most often accomplished by self-monitoring of blood glucose (SMBG) by capillary method. Atleast 3 -4 values at different times of the day is required to adjust the insulin doses especially those on basal-bolus regime to achieve stricter control. The targets of blood glucose and HbA1c of different age groups are shown in Table 4. During the last decade Continuous Glucose Monitoring Systems (CGMS) are available which may be very useful in patients with brittle diabetes to fine tune the insulin regime and diet.[8]

Monitoring and long term follow up of a child with T1 DM

- Detailed fundus examination for retinopathy once the child is 10 years of age or has diabetes for 3-5 years or more
- TSH levels for hypothyroidism every 1- 2 years
- Urine for microalbumin for nephropathy: starting once the child is 10 years of age or after 5 years of diabetes and then yearly.
- Blood pressure measurement at least once or twice a year with appropriate cuff and adjust for the age specific centiles.
- Lipid profile on at least yearly basis especially in patients with history of cardiovascular disease in the family.
- Celiac disease screen with transglutaminase antibodies or endoscopy as clinically indicated.

Psychological support

The diagnosis of diabetes is invariably a shock to the child and family. Psychological and adjustment issues may arise at diagnosis or during adolescence. Clinical psychologists or psychiatrists,diabetes nurses, other parents and local support groups play a vital role in the overall care of diabetic children. Parent and patient support groups may complement office visits. They may be informational, supportive and even therapeutic at times.[1,2,10]

Newer insulin delivery systems

Insulin therapy for diabetes is commonly delivered by vial and syringe. Though this method of delivery is cost-effective, many patients especially children with type 1 diabetes feel this as inconvenient. The use of insulin pens has minimized some of the short-comings associated with the use of vials and syringes. The advantages of using insulin pens are:

- More convenient and easy to transport than vial/syringe.
- Accurate dosing.
- Less pain in injection site due to short, fine needles (5-6mm and 30-32 gauge).
- User-friendly for patients with visual impairment (presence of audible click) and decreased fine motor skills.

Insulin pens have definite advantage in the management of diabetes in school-going children as it can be easily carried by them.[6]

Continuous Subcutaneous Insulin Infusion (CSII)

CSII or Insulin pump is the near physiological insulin delivery system currently available. In this method, insulin is delivered into the subcutaneous tissue at a selected rate using a portable electro-mechanical pump. Either regular insulin or the rapid acting analogues can be used in CSII. Using the insulin pump, a patient can set a continuous delivery of insulin throughout the 24 hours which is called the "basal" infusion and this should be superimposed by meal related insulin "boluses". Different rates of basal insulin infusion can be programmed in the pump based on the diurnal variation in blood glucose levels. All these applications are user friendly and have helped to improve the quality of life of a type 1 diabetic patient by enabling them to have a flexible life style and better glycemic control. However, the enormous cost involved in CSII therapy makes this technology beyond reach for the majority of Indian children with type 1 diabetes.

Alternative insulin delivery systems

It is the dream of almost every type 1 diabetic patient to have his or her insulin dose in a painless non-injectable method. The most widely studied alternative routes of insulin administration include:

Table 4: Blood glucose and HbA1c goals in children with type 1 DM

Age in years	Blood glucose goals (mg/dl)		
	Before meals	Bedtime/overnight	HbA_1c
0-6	100-180	110-200	<8.5%
7-12	90-180	100-180	<8.0%
13-19	90-130	90-150	<7.5%

i) Inhaled insulin ii)Oral insulin and iii)Buccal insulin. Inhaled insulin was about to be introduced in the market when it was withdrawn due to pulmonary complications. Other modes of delivery are still in the experimental stage of development.[9]

Artificial Pancreas

The basic requirement of an artificial pancreas or a closed loop system is that it should be able to sense the blood glucose levels and deliver an accurate insulin dosage based on a standard algorithm. Also, it should be able to sense hypoglycemia, have the ability to interrupt insulin infusion and to inject counter-regulatory hormone such as glucagon. The system should be able to identify the problems like sensor malfunction or block in the insulin cannula and alert the patient/ parents. When a continuous glucose monitoring system (CGMS) and CSII are interconnected by wireless transmission, and operated together, they can be made to work as a closed loop system. A fully implantable artificial pancreas system is being investigated and the short term results are providing hope for a better set of type 1 diabetic children with affordability.

Future directions

Pancreatic transplantation, Islet replacement therapy and Stem cell therapy are under different phases of evolution. These therapies, if successful, may provide a hope for complete resolution of type 1 diabetes.[9]

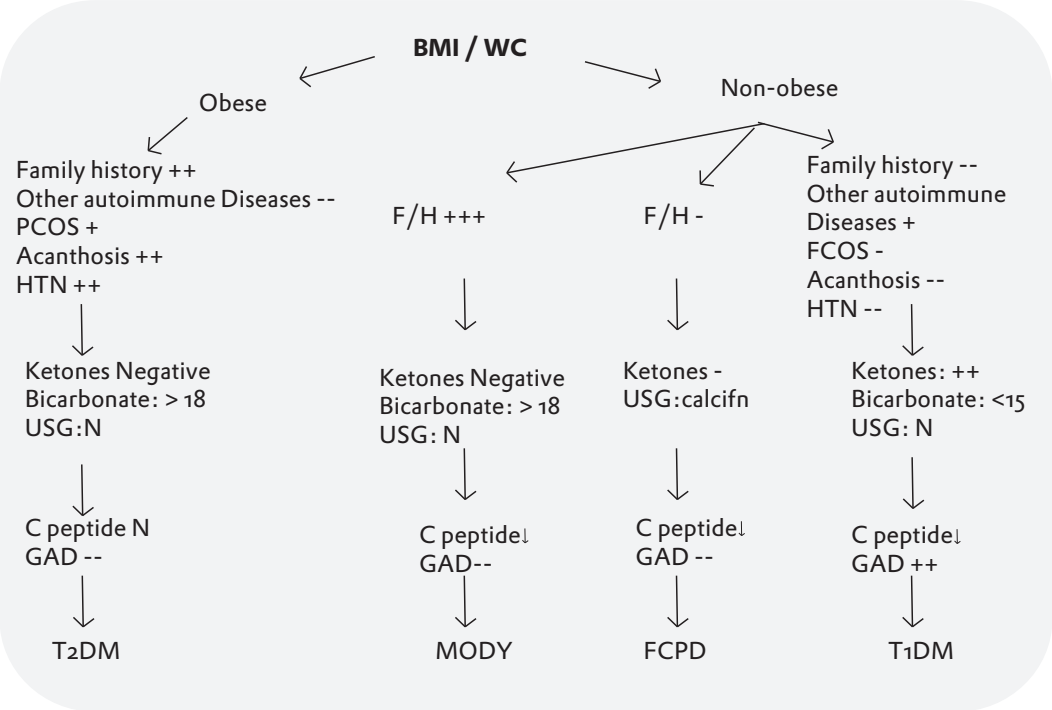
Type 2 DM in children

Cross sectional studies from all the corners of India have shown rise in childhood obesity by several folds consequent to modernization of lifestyle and unhealthy food habits. Disturbingly, in tandem with this rise in childhood obesity an increase in type 2 diabetes in children is also noted. The conditions closely associated with obesity and type 2 DM include hypertension, dyslipidemia, non-alcoholic fatty liver disease and metabolic syndrome, all of which are related to increased risk of cardiovascular disease.[11–13] Pathogenesis of type 2 diabetes is discussed in detail in the relevant section.

Clinical presentation

A small fraction of patients, may be around 10 -20% of children with type 2 DM present with ketoacidosis initially. Contrary to classic type 1 DM the beta cells recover to the extent that they do not require insulin later. This has been called 'flat bush' diabetes in literature. Hyperglycemic hyperosmolar state like in adults with type 2 DM and malignant hyperthermia like syndrome with rhabdomyolysis may also be a very rare presentation. The latter is usually associated with very poor outcome unless diagnosed very early. Typical

Fig1: Approach to Diabetes Mellitus in young



F/H - Family History
GAD - Glutamic acid Decarboxylose
HTN - Hypertension
FCPD - Fibro Calcific Pancreatic Diabetes

BMI - Body mass Index
WC - Waist Circumference
PCOS - Polycystic Ovarian Syndrome
USG - Ultra Sonography

osmotic symptoms may not occur always and one may need to screen all obese children with signs of insulin resistance and family history of diabetes to detect diabetes early. [14,15]

Diagnosis

Usually fasting and 2hr post 75 gm glucose sample is enough to diagnose diabetes. In younger children the glucose load for testing is 1.75 gm/kg (maximum of 75gm). Fasting venous plasma glucose ≥ 126 mg/dl or a 2 hour post glucose challenge value of ≥ 200 mg/dl confirms the diagnosis of diabetes. Clinical features of insulin resistance (central adiposity and acanthosis nigricans), family history of diabetes in close relatives, presence of other features of metabolic syndrome viz. hypertension and dyslipidemia and absence of other autoimmune disorders narrows down the diagnosis to type 2 diabetes mellitus. Absence of ketonuria and acidosis also rules out significant insulinopenia and favours the diagnosis of type 2 DM. Further testing including C-peptide, autoimmune markers like GAD 65 and islet cell antibodies may not be necessary always in all patients. Maturity onset monogenic diabetes (MODY) is suspected when the family history suggests more than 3 generations affected. The latter usually presents with mild hyperglycemia, especially the common MODY type 2 and respond to oral hypoglycemic agents (sulphonylureas). An algorithmic approach to diabetes mellitus in young is given in Figure 1.

When a child should be screened for type 2 diabetes

As in adults, a child who is overweight (BMI more than 90th centile) and features of insulin resistance like acanthosis nigricans and family history of type 2 diabetes should be screened. Obese adolescent girls who present with features of polycystic syndrome like menstrual irregularities, hirsutism and acne also need to be screened.

Management

This is discussed in the relevant section.

Metformin

Of the available oral anti-diabetic agents, not all are approved for Paediatric use except metformin for children with type 2 DM above 12 years of age. The main mechanism of action is decreased hepatic glucose output. Strictly, it is anti-hyperglycemic and also has modest effect on suppressing appetite and promoting weight reduction. Through its significant effect on insulin resistance, it has good effect on improving ovulatory dysfunction in girls with polycystic syndrome. Metformin should be discontinued during administration of radiocontrast agents if a patient has renal dysfunction, hepatic diseases or serious infections. Side effects are usually gastrointestinal disturbances which may improve on continued use and occasionally vitamin B12 deficiency which may need to be supplemented. The usual starting dose of metformin in an adolescent girl is 250 mg oncedaily after dinner for a week or two and then gradually up titrate to a maximum of 2000mg per day in 2 to 3 divided doses.

Insulin

If adequate glycemic control is not attained with good lifestyle measures and metformin then the child should be managed with insulin which is discussed with type 1 DM.

Maturity onset diabetes in young (MODY)

Maturity –onset diabetes of the young is a genetically and clinically heterogenous group of disorders characterized by non-ketotic diabetes. It is inherited in an autosomal dominant manner with onset usually before 25 years of age or in childhood or adolescence. Mutations in atleast[10] different varieties of genes are described under MODY. One of these genes (GCK) encodes the glycolytic enzyme glucokinase; mutations this gene causes MODY 2. The other genes encode transcription factors. Pathophysiologically, the genetic defect results in abnormalities in atleast one of the critical steps involved in insulin secretion resulting in beta cell dysfunction and hyperglycemia. Abnormalities in liver and kidney functions occur in some form of MODY, reflecting expression of the transcription factors in these tissues.

Clinically, MODY usually causes a mild hyperglycemia in a non-obese young patient with significant family history of diabetes in successive generations conforming to autosomal dominant pattern of inheritance. Being a genetic defect the mild hyperglycemia is present from childhood, though it may be picked up only when the patient is evaluated in adulthood. They usually respond to oral hypoglycemic agents and only rarely, a patient may present with rapidly progressing severe hyperglycemia necessitating insulin therapy. Absence of obesity, prominent family history and young age of presentation are few clinical clues which help in differentiating MODY from Type 2 DM.[16]

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Answer to : **Diagnose the Condition**

Discussion

ECG Shows sinus rhythm as evidenced by normal P wave axis and negative P wave in AVR lead. PR interval is normal. Occurrence of P wave is regular. But all the P waves are not followed by a QRS complex. Alternate P wave is not conducted. QRS complex shows RBBB pattern with right axis deviation.

Final diagnosis – MOBITZ TYPE 2 AV BLOCK WITH RBBB.

- Dr. M.Chokkalingam, Consultant Cardiologist, CSSH.

Review Article

Diabetes in Pregnancy

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Abstract

Diabetes is one of the commonest medical complications of pregnancy. It could antedate pregnancy or be identified for the first time during pregnancy when it is termed Gestational diabetes mellitus(GDM). GDM is plagued by controversies right from screening, diagnosis and interventions. Identification of GDM is important as it impacts maternal health care during and after pregnancy. Following Hyperglycemia and Adverse Pregnancy Outcomes (HAPO) study and International Association of Diabetes and Pregnancy Study Groups (IADPSG) recommendations, a new screening and diagnostic criteria seems to be gaining consensus around the world. As India is fast catching up with China to become the diabetic capital of the world, thrust is now on universal early testing in our populations at the first prenatal visit. Diabetes in Pregnancy Study Group India (DIPSI) has also suggested cost effective method of screening in resource-challenged communities. GDM offers an excellent opportunity for primary prevention of Diabetes, as the mothers are at increased risk of future diabetes, predominantly type 2 diabetes, as are their children.

Key Words : Diabetes in Pregnancy, Gestational diabetes mellitus, Guidelines, Hyperglycemia and Adverse Pregnancy Outcomes

Chettinad Health City Medical Journal 2012; 1(4): 177 - 181

Introduction

GDM is defined as glucose intolerance that is first recognized during pregnancy. The prevalence of GDM corresponds to the prevalence of IGT within a given population. It ranges from 1.4% to 2.8% in low risk populations to 6-10% in high risk populations[1,2]. The prevalence is higher among Asian women compared to the whites (8.7% vs 3.9%).The so-called Asian Indian Phenotype refers to certain unique clinical and biochemical abnormalities in Indians which includes increased insulin resistance, higher waist circumference despite lower body mass index. This phenotype makes Indians more prone to diabetes. Maternal hyperglycemia mild or severe has an adverse impact on maternal health such as risk of operative deliveries, gestational hypertension and preeclampsia. Perinatal morbidities may include macrosomia, birth trauma, hypoglycemia, hyperbilirubinemia, polycythemia etc[3]. Women known to have diabetes must control their blood glucose (HbA1c < 6.3%)[4] before planning conception. The present review article shall focus more on defining GDM, its present day relevance, screening, and diagnostic criteria.

The Indian Scenario

India would be having the highest population of diabetes by 2025.[5] The increased prevalence is attributed to improved life expectancy, urbanization, changing dietary habits, the obesity epidemic, and physical inactivity.[6]Studies from various parts of India reports prevalence of 6% to 18.8%. In a national survey for the prevalence of GDM we found 16.55% of pregnant women having 2-hour PPG 140mg/dl, which was closer to the prevalence of IGT in our country. (Urban > Rural).[7] The obesity epidemic has compounded the problem. The prevalence of GDM in underweight (BMI-13-18.4) is 0.7%, normal weight (18.5-24.9) is 2.3%, overweight (25-29.9) is 4.8%, obese (30-34.9) is 5.5% and in extremely obese (35-64.9) is 11.5%.

Definition

In 2010, the IADPSG, an international consensus group with representatives from multiple organizations, recommended a change in the terminology.

In this, diabetes diagnosed during pregnancy is classified as overt or gestational. ADA endorsed this in 2011.[8,9]

Overt diabetes: At the first antenatal visit, if a woman has a fasting plasma glucose (FPG) ≥ 126mg/dl or HbA1c ≥ 6.5% or a random plasma glucose ≥ 200 mg/dl.

Gestational diabetes: Women who have FPG ≥ 92 mg/dl but <126 mg/dl at any gestational age GTT at 24-28 weeks –with at least one abnormal value:FPG ≥ 92 mg/dl but < 126 mg/dl One hour ≥ 180 mg/dl or two hour ≥ 153mg/dl

Pathophysiology

Pregnancy is normally associated with progressive insulin resistance beginning from midpregnancy through to term. It arises from increased maternal adiposity and the placental hormones namely, human placental lactogen, placental growth hormone variant, cortisol, progesterone etc. This puts an added strain to the beta cells to compensate for the insulin resistance. Those who are unable to do so develop glucose intolerance. In women with GDM, these physiological changes are superimposed on underlying chronic insulin resistance and beta cell dysfunction. This also explains higher prevalence for GDM in women with polycystic ovarian syndrome.

Whom to screen?

The screening strategies that range from selective targeted screening of moderate to high risk individuals to universal screening depends on the prevalence of diabetes in that population (IADPSG). The relative risk of developing Gestational Diabetes Mellitus in Asian Indian women is 11.3 times compared to White women. This necessitates universal screening for gestational diabetes during pregnancy in India as recommended by DIPSI.[10]

In population with lower diabetes prevalence, timing of screening depends on the risk profile. Women at high risk are offered screening at first antenatal visit, moderate risk at 24-28 weeks.(ADA)

Low-risk status

- Age <25 years.
- Normal BMI.
- Member of an ethnic group with a low prevalence of gestational diabetes mellitus .
- No known diabetes in first-degree relatives .
- No history of IGT.
- No history of poor obstetric outcome

High risk status

- Age> 25 years
- Obese / overweight
- Strong family history of diabetes
- Previous h/o macrosomia/foetal loss
- Persistent glycosuria
- Past h/o IGT / GDM
- Ethnic group with higher prevalence of DM
- H/o polyhydramnios / stillbirths / congenital anomalies.

When and how to screen?

ADA had earlier recommended a 2 step procedure at 24-28 wks

a) 50 gm GCT without regard to the time since last meal

b) If >140 mg/dl, 100 gm GTT to be offered. If 2 or more values are abnormal GDM is diagnosed.

	NDDG (1979)	CC (1982)12
Fasting	> 105 mg/ dl,	> 95
1 hour	> 190 mg/dl,	> 180
2 hours	> 165 mg/dl,	> 155
3 hours	> 145 mg/dl.	> 140

NDDG :National Diabetes Data Group, CC: Carpenter and Coustan

The IADPSG recommends 75 gm two hour GTT and the thresholds are based on the HAPO study. The Hyperglycemia and Adverse Pregnancy Outcomes (HAPO) study[11] was a large multinational epidemiologic study, involving 25,505 pregnant women at 15 centers in nine countries. These women underwent 75-g oral glucose-tolerance testing at 24 to 32 weeks of gestation. This was designed to examine the effects of milder maternal hyperglycemia and adverse outcomes mentioned below. Multiple logistic regression was used to examine associations of GDM and obesity with outcomes.

It demonstrated that risk of adverse maternal, foetal, and neonatal outcomes continuously increased as a function of maternal glycemia at 24-28 weeks, even within ranges previously considered normal for pregnancy. For most complications, there was no threshold for risk.

75 gm GTT- FPG ≥ 92, 1 hr ≥ 180 , 2 hr ≥ 153 mg/dl. Any one abnormal value defines GDM.

The lower cutoffs were determined by the average glucose values at which risk for

- Birth weight > 90th centile
- Cord C-peptide > 90th centile
- Percent body fat > 90th centile
- Preeclampsia Increased by 1.75- 2 times, compared to mean glucose values

Preterm delivery and need for Caesarean - section increased by 45%

By applying this new criteria, the incidence of GDM would go up to 17.8% because only one abnormal value, not two, is sufficient to make the diagnosis. The diabetic associations around the globe recognize the anticipated overdiagnosis and "medicalization" of pregnancies previously categorized as normal. There are few data from randomized clinical trials for being modest[16,17] IADPSG - 2010 recommendations are endorsed in the ADA position statement in Jan 2011. [8,9]

Two discrete phases: The first is detection of women with overt diabetes not previously diagnosed or treated

outside pregnancy. Universal early testing in populations (with a high prevalence of type 2 diabetes) is recommended at the first prenatal visit. The second phase is a 75-g OGTT at 24-28 weeks gestation in all women not previously found to have overt diabetes or GDM.

DIPSI Recommendations: DIPSI has suggested a one step procedure with a 2 hour plasma glucose after a 75 gm glucose load without regard to time of the last meal. A 2 hr plasma glucose >140 mg/dl defines GDM, if it is 120-139 mg/dl it is termed Gestational glucose intolerance (GGI). If the test is normal, test repeated at 24-28 wk and then 32-34 wks.[10]

Maternal and Foetal complications in Pregestational and GDM

Maternal Complications include risk of abortions, chorioamnionitis, preeclampsia, postpartum bleed, higher rates of Cesarean section. In pregestational diabetes, there could be progression of diabetic nephropathy and retinopathy, higher insulin requirements and higher mortality if previously affected by CAD or cardiomyopathy. Foetal effects include congenital anomalies such as Transposition of great vessels, septal defects, hypoplastic LV, CNS anomalies like spina bifida, anencephaly, neural tube defects, caudal regression syndrome, genitourinary anomalies, anorectal atresia etc.

Other effects include macrosomia, foetal demise during the last 4-6 weeks.

Neonatal complications include respiratory distress, hypoglycemia, hypocalcemia, hyperbilirubinemia, polycythemia etc.

Preconceptional Care

All women with either Type 1 or 2 diabetes planning pregnancy must be counseled about the need to achieve a good glycemic control (A1c<6.3%) to reduce the risk of congenital anomalies and spontaneous abortions.[4] They must be screened for retinopathy and microalbuminuria before planning pregnancy. Eye testing is recommended in all the trimesters of pregnancy. They must be instructed to follow diet and regular exercises. Those on oral hypoglycemic agents, ACE inhibitors or ARBs, statins, fibrates or beta blockers need to change their medications.[4] Pregnancy is risky for those with advanced nephropathy / retinopathy or CAD or severe hypertension. Staring an insulin regimen before conception allows women to become familiar with insulin self administration and dose adjustment.

Management

A multidisciplinary approach is required comprising obstetrician, diabetologist, diabetic educator, dietician and a pediatrician.

Target blood glucose levels : To maintain a mean plasma glucose level of 105-110 mg/dl for a favourable
obstetrician, diabetologist, diabetic educator, dietician and a pediatrician.

Target blood glucose levels : To maintain a mean plasma glucose level of 105-110 mg/dl for a favourable foetal outcome, it is desirable to have fasting glucose <90 and 2 hour post prandial < 120mg/dl respectively. The recommendations are:

ADA(capillary glucose) –premeal ≤ 95, 1hrPP ≤ 140 and 2hr PP ≤ 120mg/dl

5th international workshop-premeal <96, 1hrPP<140 and 2 hrPP<130 mg/dl

A) Medical nutrition therapy (MNT)

Goals : To achieve normoglycemia, prevent ketosis and provide adequate weight gain. MNT is tried for two weeks.

- 3 meals and 3 snacks pattern, a bedtime snack must to prevent ketosis in fasting state
- Ideally split breakfast into two portions to avoid peaking of plasma glucose due to Dawn phenomenon
- Carbohydrates restricted to 40-45%. Carbohydrate counting to be practiced, low glycemic index foods to be chosen
- Underweight : 36-40 kcal/kg , 12.5-18 kg wt gain
- Ideal body weight: 30 kcal/kg , 11.5-16 kg
- Overweight : 24 kcal/kg , 7-11.5 kg
- Obese : 12-18 kcal/kg, 6 kg
- All must continue folate and iron and vitamin D as indicated.
- Recommended protein -1.1g/kg
- More than 90% patients can be managed with MNT(DIPAP)[10]

B) Physical activity

Planned physical activity of 30 minutes /day. One could do arm exercises /walk briskly for 10 minutes after each meal. Upper body exercises are always preferred.

C) Pharmacological therapy

Insulin: The safest therapeutic option in those failing MNT(category A). If the FPG>120 mg/dl or PP>199 mg/dl, insulin is initiated along with MNT.
Human insulins (both short and intermediate acting)can be given as a basal bolus regimen or as a premixed insulin(30/70 or 50/50).

Role of Insulin Analogs

Rapid using insulin analogs like Lispro and Aspart (both category B) can be considered if the postprandial glucose is not under control. Premixed analogs have also been found to be safe.

Role of Insulin Analogs

Rapid using insulin analogs like Lispro and Aspart (both

category B) can be considered if the postprandial glucose is not under control. Premixed analogs have also been found to be safe.

Long acting analogs like Glargine (Category C) and Detemir(FDA category B) have also been approved.
Women with pregestational diabetes require more insulin than those with GDM. If insulin requirement drops it could mean placental dysfunction or foetal jeopardy or increased glucose utilization by the macrosomic fetus.

Oral hypoglycemic agents

a) Glibenclamide: Of the sulphonylureas, this crosses the placenta the least (foetal concentration<1% of maternal levels). A randomized unblinded clinical trial on 404 GDM patients compared glyburide vs insulin. The OHAs was initiated after the 1st trimester. There was no difference in the perinatal outcomes[13].

b) Metformin: More recent studies have found it to be safer, with no perinatal complications. Continuing metformin in women with PCOS after conception throughout pregnancy is being favoured by few studies. Those on metformin required lesser insulin and had lesser weight gain.[14]

Monitoring glycemic control

HbA1c level tested in early pregnancy is helpful to differentiate between an overt diabetic and GDM. If the value is more than 6%, she is likely to have overt diabetes. HbA1C as a tool in monitoring the glycemic control during pregnancy may serve as a prognostic value. It is not routinely recommended in the second and third trimesters of pregnancy. If HbA1C level is used to monitor glucose control in pregnancy, the target level to be maintained is 5.3%, which corresponds to a fasting blood sugar level of 90 mg/dl and 2-h post-meal level of 120 mg/dl[18].

Self monitoring of blood glucose (SMBG) is encouraged 4 times daily(fasting/1hr or 2hr PP) once a week. Postprandial monitoring is found to be superior to premeal monitoring – better HbA1c, lower LGA and lower rate of Cesarean Section. The mothers also need to be taught self dose adjustment. Continuous glucose monitoring system (CGMS) may be required only in those cases where sugars are difficult to control.[15]

Foetal Surveillance: Ultrasound: baseline, 20 week anomaly scan, from 26 weeks onwards for growth and liquor volume.

- 3rd Trimester : Abdominal : Head Circumference Ratio checked.
- Maternal monitoring of foetal activity

The nonstress test (NST), Doppler umbilical artery velocimetry

Timing of delivery: before full term is not indicated unless for obstetric indication-(Pre eclampsia, IUGR) , macrosomia and polyhydramnios.

Labour; Control maternal glucose levels during labour to prevent foetal hyperinsulinemia, acidosis and neonatal hypoglycemia

- <70 mg/dl – Dextrose Normal Saline (DNS) 100 ml/hr
- 90-120 mg/dl – Normal Saline (NS) 100ml/hr, CBG every 1-4 hourly intervals
- Regular Insulin given as infusion only if glucose >140 mg/dl.
- Post delivery keep patients on DNS

Neonatal management – Monitor for respiratory distress, check capillary glucose 1, 2 and 4 hrs after birth and after feeding. Early breast feeding is encouraged.

- Post partum period: Insulin sensitivity improves and insulin requirements drop.
- 75 gm OGTT offered 6-12 weeks post partum – if normal, it should be repeated after 6 month and annually. Women should be counseled about their future risk for diabetes.

Conclusions

Gestational diabetes offers a good opportunity for primary prevention of diabetes not only in the mother but also her offspring. A short term intensive care ensuring good glycemic control, good maternal nutrition and a normal birth weight of the baby gives a long term payoff in the prevention of obesity, impaired glucose tolerance and diabetes in the baby. This can be ensured only by a committed team of obstetrician, diabetologist and pediatrician.

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Let there be "blue" light!

Skin and soft tissue infections are the second most common infections encountered in clinical practice. Treatment of these is becoming more and more difficult due to emergence of antibiotic resistant strains. One enzyme in particular, NDM-1, makes some bacteria resistant to almost all antibiotics. Some researchers are apprehensive that the antibiotic era as we know of it may be coming to an end and we might be gazing down a dark tunnel. But a recent animal study done at Harvard Medical school hints at the presence of light at end of the tunnel and the colour of that light is blue. In that study the researchers used two groups of animals infected with P. Aeroginosa: one group was treated withblue lightwhile the other acted as control. The animals treated with blue light recovered completely whereas 82% of animals died among the controls. The study has shown that the "blue" light can selectively eradicate P. Aeroginosa infection without damaging the skin. The results will be published in the March 2013 issue of Antimicrobial Agents and Chemotherapy.

- Dr. K. Ramesh Rao

Review Article

Management of Hyperglycaemia in the Hospital Setting

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Abstract

Hyperglycaemia can occur in patients with known or undiagnosed diabetes, or it may occur during acute illness in those with previously normal glucose tolerance (stress Hyperglycaemia). Hyperglycaemia in hospitalized patients is a common problem with serious medical and financial consequences. Hyperglycaemia as well as hypoglycemia has been shown to worsen morbidity and mortality rates in Intensive care unit (ICU) and non-ICU settings. Though tight glucose control has been shown to improve mortality rates in surgical ICU setting, similar results could not be achieved in medical and mixed ICUs. There are no similar large randomized control trials (RCTs) done in general medical and surgical wards. The failure to show good results with intensive therapy is partly attributable to higher frequency of hypoglycemic episodes.

American Diabetes Association- American Association of Clinical Endocrinologists (ADA –AACE) guideline recommends that IV insulin infusion should be used to control Hyperglycaemia in the majority of critically ill patients in the ICU setting, with a starting threshold of no higher than 180 mg/dl (10.0 mmol/l) and the glucose level should be maintained between 140 and 180 mg/dl (7.8 and 10.0 mmol/l). For the non-critically ill patients in the general ward, ADA-AACE guideline suggests a consensus target value of pre-meal glucose below 140 mg/dl and random BG value below 180 mg/dl, preferably using subcutaneous insulin (basal and prandial insulin and a supplemental correctional insulin dose to counter pre-meal Hyperglycaemia). Using standardized protocols in general wards may improve outcomes.

Key-words: Diabetes mellitus, Intensive care unit, Hyperglycaemia, Hypoglycemia, Glucose variability, ICU mortality, Intensive insulin therapy

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Introduction

Hyperglycaemia in hospitalized patients is a common problem with serious medical and financial consequences. In a study done in tertiary care hospitals in South Asian countries including India, hospital admission expenditure for diabetic in patients with no complications ranged from 11 to 75% of per-capita income.[1]

Hyperglycaemia can occur in patients with known or undiagnosed diabetes, or it may occur during acute illness in those with previously normal glucose tolerance (stress Hyperglycaemia). However, irrespective of the cause, Hyperglycaemia is known to be associated with poor outcomes.[2, 3]

This article attempts to present in brief, the data on glycemic control and outcomes in critically ill and non critically ill hospitalized patients, the management of Hyperglycaemia in ICU and non-ICU setting, and general guidelines for transitioning from the critical care units to the regular hospital units and then to home.

Hyperglycaemia and outcome in medical and surgical ICUs

Hyperglycaemia has been noted to be associated with adverse outcomes in both ICUs as well as in general medical and surgical wards. This was illustrated by a retrospective cohort study of 1826 medical and surgical ICU patients. Compared to patients who survived, those who died had significantly higher mean blood glucose levels (172 versus 138 mg/dL), and maximum blood glucose levels (258 versus 177 mg/dL) and analysis of glucose values added predictive power above that achieved by APACHE II scores alone. There was a graded effect, with higher mortality among patients who had higher blood glucose levels. Mortality ranged from 9.6 percent in patients with mean blood glucose between 80 and 99 mg/dL to 42.5 percent in patients with a mean blood glucose greater than 300 mg/dL.[2]

Several randomized control trials (RCTs) have been published evaluating intensive and less stringent glycemic control in medical and surgical ICUs. In one of the landmark RCTs done in surgical ICUs by van den Berghe et al, intensive insulin therapy targeting arterial glucose levels of 80 –110 mg/dl was compared with conventional therapy targeting glucose levels of 180-200 mg/dl among 1500 patients, 13% of them with established diabetes. They achieved mean target glucose levels of 103 vs 153 mg/dl. There was a 42% relative risk reduction in ICU mortality, significantly

lower rates of dialysis and septicemia, as well as a reduced need for blood transfusion and ventilatory support with intensive therapy as compared to conventional therapy.[4] However, in a later study, when the same researchers implemented a similar protocol for glucose control in 1,200 medical ICU patients, they failed to achieve a significant reduction in mortality despite achieving similar mean glucose level as in their previous study in surgical ICU. This unexpected outcome was attributed partly to the 6-fold increase (18.7 vs. 3.1%) in hypoglycemic events (BG <40 mg/dl) in the intensively treated group.[5]

VISEP trial compared conventional with intensive insulin therapy and colloid with crystalloid infusion in ICU patients with severe sepsis. There was no significant decrease in 28-day mortality (24.7% vs 26%) but higher rates of severe hypoglycemia (BG <40 mg/dl) with intensive insulin therapy in patients with severe sepsis (17 vs. 4.1%; P < 0.001).[6] Another study on 504 patients in a mixed medical and surgical ICU showed that intensive glycemic control, achieving similar blood glucose targets as in van den Berghe's study (mean 115 vs 145 mg/dl), did not result in a decrease in morbidity or 28-day mortality (36.6% vs 32.4%), while increasing the rate of hypoglycemia fivefold.[7]

The largest study to date, NICE-SUGAR study, compared tight glycemic control (80-110 mg/dl) with relaxed control (<180 mg/dl) among 6,104 patients in a mixed ICU setting.[8] The 90-day mortality was significantly higher in the intensively treated versus the conventionally treated group (78 more deaths; 27.5 vs. 24.9%; P <0.02) in both surgical and medical patients. Higher mortality risk in intensively treated group persisted when surgical and medical patient subgroups were separately analyzed (OR 1.31 and 1.07, respectively; P=0.10). The intensively treated group had more CV related mortality (76 more deaths; 41.6 vs. 35.8%; P <0.02), as well as incidence of severe hypoglycemia (6.8 vs. 0.5%; P <0.001)[8].

A recent meta-analysis of RCTs reported comparisons between intensive insulin therapy with glycemic targets of 72–126 mg/dl (4.0 –7.0 mmol/l) and less intensive therapy with targets of <150 to 220 mg/dl (<8.3–12.2 mmol/l) among 8,432 critically ill patients. Intensive therapy as compared to conventional therapy, did not significantly improve mortality rate (21.6 vs. 23.3%) or dialysis rate while resulting in a fivefold increase in hypoglycemia (13.7 vs. 2.5%)[9]. There was also no significant difference in mortality when stratified by glucose goal (very tight: < or = 110 mg/dL; or moderately tight: < 150 mg/dL) or by intensive care unit setting - surgical or medical. However a decrease in septicaemia was observed in the intensive therapy group.[9] In a second meta-analysis of 13,567 critically ill patients including NICE-SUGAR data, only patients in surgical ICUs appeared to benefit from intensive insulin therapy (RR 0.63, 95% CI 0.44–0.91); patients in the other ICU settings did not (medical ICU: RR 1.0, 95% CI 0.78–1.28; mixed ICU: RR 0.99, 95% CI 0.86–1.12). But intensive therapy resulted in a sixfold increase in the rate of hypoglycemia in all ICU patients. The different targets of intensive insulin therapy (glucose level ≤ 110 mg/dl or ≤ 150 mg/dl) did not influence either mortality or risk of hypoglycemia.[10]

Hyperglycaemia and outcome in patients with acute myocardial infarction

Diabetic patients with acute myocardial infarction (AMI) have a relatively high mortality rate in the 1st year following the episode. In DIGAMI study, insulin-glucose infusion in the 1st 24 hours followed by multi-dose subcutaneous insulin for ≥ 3 months was s compared to conventional therapy in 620 patients wit h AMI . Ther e wa s 29 % relativ e reductio n i n 1-yea mortality in the infusion group. The subgroup (within insulin infusion group), who had a low cardiovascular risk profile and no previous insulin treatment had an even better mortality reduction (52%).[11] However, DIGAMI 2 study, a multi-centre RCT of 1,253 patients with AMI and diabetes, failed to show a decrease in

Table 1: Major RCTs evaluating intensive insulin therapy in ICU patients #

Study (year) [ref]	n	setting	Mean Glucose level achieved(mg/dl)		Primary outcome	RRR (%)	Odds Ratio (OR)
			Intensive group	Control group			
DIGAMI] (1995)[11]	620	CCU (AMI)	173	211	1 yr mortality	29	NR
Van den bergh et al (2001)[4]	1548	SICU	103	153	ICU mortality	42.00%	0.58 (0.38-0.78)
DIGAMI 2 (2005)[12]	1253	CCU (AMI)	164	180	2 yr mortality	Not significant	NR
Van den bergh et al (2006)[5]	1200	MICU	111	153	hospital mortality	7	0.94 (0.84-1.06)
NICE SUGAR (2009)[8]	6104	Mixed ICU	115	145	90 days mortality	-10.6	1.14 (1.02-1.28)
VISEP (2008)[6]	537	ICU	112	151	28 day mortality	5	0.89 (0.58-1.38)

- Table adapted from Moghissi et al. Diabetes care 2009 [15], NR-not reported

mortality with similar intervention.[12] Another study (Hyperglycaemia Intensive Insulin Infusion in Infarction (HI-5)) showed only improvement in incidence of congestive heart failure and reinfarction at 3 months in the intensively treated group without any significant difference in mortality.[13]

Summary of ICU studies

While the initial study by van den Berghe and colleagues[4] in surgical ICU patients reported remarkable benefit with intensive insulin therapy (target 80-110 mg/dl), consistently positive results could not be achieved in other trials involving medical and mixed ICU patients(Table 1). Actually the largest study published so far showed increased mortality with intensive insulin therapy (NICE-SUGAR). The reasons could be manifold. The positive results reported in the initial studies might be attributable to

1) Differences in measurement and reporting of blood glucose values.
2) Selection of participants (medical ICU, post MI, elective or emergency surgery).
3) Glycaemic variability and fluctuations in an individual patient despite achieving a good average glucose level.[14]
4) Variations in nutritional support between studies.
5) Also some of the later studies had relatively tighter targets even in control group, probably already approaching optimal glucose levels, thus not allowing room for additional improvement with tighter control.

ADA-AACE guideline[15] recommends that insulin infusion should be used to control Hyperglycaemia in the majority of critically ill patients in the ICU setting, with a starting threshold of no higher than 180 mg/dl. Once IV insulin therapy has been initiated, the glucose level should be maintained between 140 and 180 mg/dl. Greater benefit may be realized at the lower end of this range (140-150 mg/dl).[15]

Hyperglycaemia and outcome in non-critically ill subjects

In adult patients admitted to general surgical and medical wards, Hyperglycaemia is associated with prolonged hospital stays, increased rate of infection, disability after hospital discharge, and death.[16, 17] In a retrospective study of 2030 adult patients admitted to a community hospital, mortality was significantly higher in patients with newly diagnosed Hyperglycaemia and those with known diabetes than in those who were normoglycemic (16, 3, and 1.7 %, respectively; P < 0.01) [16]. Hyperglycaemia at admission has also been associated with worse outcomes in patients with community-acquired pneumonia.[17]

Target Glucose levels in non-critically ill subjects

There are no RCTs establishing specific targets for glucose control in the non-critically ill hospitalized patients. ADA/AACE guideline in 2009[15] suggests a consensus target value of pre-meal glucose below 140 mg/dl and random BG value below 180 mg/dl, in general. Modification of the regimen is necessary when BG values are <70 mg/dl. Occasionally, a higher glucose range may be acceptable in terminally ill patients or in patients with severe co-morbidities, as well as when frequent glucose monitoring or close nursing supervision is not feasible.[15]

Treatment Options for achieving optimal glycemic targets

In the hospital setting, insulin therapy is the preferred method for achieving glycemic control in most clinical situations. Insulin inhibits free fatty acids, pro-inflammatory cytokines, adhesion molecules, chemokines and inflammatory growth factors, all of which may be detrimental in critically ill patients. Many of these pro-inflammatory pathways involve the transcriptional factor, nuclear factor-NF-kappa beta (NF-kB). The mechanisms of insulin regulation of these factors are complex, although predominantly insulin seems to have a direct suppressive effect on (NF-kb). Furthermore, insulin enhances nitric oxide synthesis, which promotes vasodilation[18].

Insulin infusion in ICU setting

In the ICU, IV infusion is the preferred route of insulin administration, because the dose can be titrated more rapidly than the dose of oral agents and it does not have a dose ceiling. Also hypoglycemia, if it occurs, is quickly reversible on stopping the infusion. Many protocols have been evaluated and validated for use in critical care setting.[19] Among them, those dynamic protocols which take into account rate of change in glucose levels in choosing insulin infusion rate are better.[20] Frequent monitoring of glucose levels (usually hourly) is needed to minimize the risk of hypoglycemia.

Patients on enteral and parenteral feeding

The glucose levels in patients receiving continuous enteral tube feeding are optimally managed mainly with the use of basal insulin, with correction doses of regular insulin added as needed every 6 hours. A recent study compared sliding-scale regular insulin (SSI) alone or in combination with insulin glargine in patients on enteral nutrition. NPH insulin was added in the 'SSI alone' group if glucose level remained persistently elevated above 180 mg/dl. Though both groups achieved similar mean glucose values (160 mg/dl vs 166 mg/dl, p=0.71), 48% of patients in 'SSI alone' group required the addition of NPH to achieve glycemic targets.[21]

Hyperglycaemia is very common in patients receiving total parenteral nutrition (TPN).[22] In those patients, regular insulin can be added to the intravenous bags; the dose is gradually titrated in increments of 5 to 10 U per litre to achieve glycemic control.

Patients on corticosteroid therapy

Recommended approach is to monitor glucose for at

at least 48 h in all patients receiving high-dose glucocorticoid therapy and to initiate insulin therapy as appropriate.[23] Glucocorticoids can cause marked Hyperglycaemia in the postprandial state. Therefore, these patients frequently require higher prandial doses of insulin than basal doses. During corticosteroid tapers, insulin dosing should be proactively adjusted to avoid hypoglycemia.

Transition from ICU to general ward

Patients who receive IV insulin infusions will usually require transition to subcutaneously administered insulin (SC insulin) when they begin eating regular meals or are transferred to lower-intensity care. Typically, a percentage (usually 70– 80%) of the total daily IV infusion dose is proportionately divided into basal and prandial components (usually 50:50 ratio, unless prandial component needs to be reduced due to poor intake).[24,25] SC insulin must be started 1– 3 h before discontinuation of IV insulin therapy in order to prevent Hyperglycaemia.

Treatment in non-ICU setting

In the general medical and surgical wards, subcutaneous administration of insulin is the preferred method for achieving and maintaining glucose control in patients with diabetes or stress Hyperglycaemia.

However, where resources permit, continuous IV insulin infusion may be used. The preferred subcutaneous insulin regimen for inpatient glycemic management includes two different insulin preparations administered as basal bolus insulin therapy, frequently in combination with a correction (supplemental) insulin scale [Table 2].

The basal component requires administration of an intermediate or long-acting insulin preparation once or twice a day. The bolus or prandial component requires the administration of short- or rapid-acting insulin administered in coordination with meals or nutrient delivery. For patients who are not eating, basal insulin is continued once daily (glargine or detemir) or twice daily [detemir /neutral protamine Hagedorn (NPH)] plus correction doses of a rapid insulin analog (aspart, lispro, glulisine) or regular insulin every 4- to 6-h interval as needed.

Whenever pre-meal glucose level exceeds >140 mg/dl, adjustable supplementary doses ("correction" insulin) of short /rapid acting insulin/analog may be added to the already scheduled prandial insulin. Correction insulin is customized to match the insulin sensitivity for each patient. Most standardized order sets for subcutaneous insulin provide several different correction-dose scales to choose from, depending on the patient's weight or total daily insulin requirement.[26]

Table 2: General guidelines for starting subcutaneous insulin in non-critically ill patients

Hold oral anti-diabetic drugs on admission, if already patient is taking

Starting total daily insulin dose

- 0.4 units/kg of body weight/day when the admission or mean blood glucose concentration is between 140 and 200 mg/dl
- 0.5 units/kg of body weight/day when the admission or mean blood glucose concentration is between 201 and 400 mg/dl
- Lower insulin doses (0.3 units/kg of body weight/day) should be given to elderly patients or those with renal failure (glomerular filtration rate < 60 ml/min)
- Patients already on insulin may be started at the same amount as their outpatient insulin dose, unless decreased intake is expected
- Half of total daily dose will be given as basal insulin and half as rapid-acting insulin.
- Rapid-acting insulin should be given in three equally divided doses before each meal. Hold rapid-acting insulin if a patient is not able to eat

Supplemental doses of rapid-acting insulin are given in addition to the mealtime insulin to correct Hyperglycaemia , selected as per patient's insulin sensitivity (as in table below)

Supplemental Insulin Protocol
BEFORE MEAL. Number of units to be added to scheduled insulin dose
BEDTIME. Give half of supplemental insulin

Blood Glucose (mg/dl)	Insulin sensitive	Usual	Insulin resistant
141-180	2	4	6
181-220	4	6	8
221-260	6	8	10
261-300	8	10	12
301-350	10	12	14
351-400	12	14	16
>400	14	16	18

The basal insulin dose is adjusted depending on the fasting glucose and the overall glucose profile. About 50% of the supplemental dose of insulin given in a day can be incorporated into the basal insulin dose for the next day. Adjustments of prandial insulin doses are based on the level of postprandial glycemia, as reflected by the blood glucose level measured before the midday meal and at bedtime.

Prolonged therapy with Sliding scale Insulin (SSI) as the sole regimen without basal insulin cover is not recommended. It is ineffective in the majority of patients (and may lead to ketoacidosis & hypoglycemia).[27, 28]

As the primary medical problem gets resolved and associated complications such as sepsis improve , glycemic control will improve, necessitating adjusting and tapering the insulin dosage on a day-to-day basis.

Role of oral agents

Oral anti-hyperglycemic agents have a limited role in the inpatient setting and agents like Metformin should be avoided due to the possibility of worsening renal function, hypotension, coexisting sepsis and the possible need for imaging studies with contrast agents. Thiazolidinediones may aggravate fluid overload and precipitate heart failure in some patients. Long acting sulphonylureas should be avoided, where fluctuation in food intake is expected. However, in selected patients, particularly patients who are not critically ill, whose condition is stable, and who are expected to have consistent meal pattern, it is reasonable to continue oral therapies.

Blood glucose monitoring

Patients treated with continuous IV insulin generally require 1 hourly testing initially and later testing frequency can be decreased to every 2h after blood glucose levels become stable. All patients enteral or parenteral nutritional support should undergo glucose testing every 4–6 h. Blood glucose testing can be discontinued in patients without a prior history of diabetes, if glucose values are consistently <140 mg/dL (< 7.8 mmol/L) without insulin therapy for 24–48 h after desired caloric intake is achieved. For patients who are able to eat, glucose measurement is usually performed four times a day: before meals and at bedtime. HbA1c needs to be checked in all patients with Hyperglycaemia (BG>140 mg/dl), especially to guide treatment decisions at the time of discharge.

Discharge Recommendations

Patients with Hyperglycaemia but HbA1C < 6.5% during admission most probably had stress Hyperglycaemia and can usually be discharged without any oral anti-diabetic (OAD) medications. Those who were taking oral anti-hyperglycemic medications and who had a high HbA1c level at the time of admission (suggesting sub-optimal control with oral drugs) should be given a more intensive treatment regime at including shifting to basal insulin plus OADs, or biphasic insulin twice daily or basal-bolus regimens. In those who were newly diagnosed to have diabetes and requiring not more than 20-25 units of insulin per day may be considered for change to oral anti-hyperglycemic drugs. Diabetes education and counselling on Medical Nutrition Therapy (MNT) should be provided to all patients with newly diagnosed diabetes. Outpatient treatment regimen, glucose monitoring techniques and sick-day guidelines should be discussed before discharge.

Areas for further research

Some of the questions needing definitive answers include optimal glycemic targets in non-critically ill patients in medical and surgical wards, optimal glycemic targets in different sub-groups of ICU patients, long-term effects of severe hypoglycemic episodes, effects of glycemic variability during hospital admission and role of continuous glucose-monitoring systems in inpatient settings.

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Review Article

Diabetes & Dental diseases

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Abstract

Diabetes is a metabolic disorder that can affect every aspect of life including the oral cavity. Dental problems in diabetic individuals are so rampant that periodontitis is considered as the sixth complication of diabetes. The objective of this review is to highlight the dental problems frequently seen in diabetes and the importance of maintaining the oral health care of diabetic individuals.

Key-words: Diabetes, Periodontitis, Xerostomia, Dental caries, Lichen planus

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Diabetes mellitus, is a group of metabolic diseases in which there is an abnormal elevation of blood glucose levels, either because of the autoimmune destruction of insulin producing beta cells of islets of Langerhans or peripheral resistance to insulin action. This high blood sugar produces the classical symptoms of polyuria (frequent urination), polydipsia (increased thirst) and polyphagia (increased hunger).[1]

Diabetes mellitus arguably has become the most significant pandemic in the last 30 years. Increasing prevalence of diabetes mellitus, along with its co-morbidities, in the population has made it an important public health issue. Phase one results of the Indian Council of Medical Research – India Diabetes (ICMR-INDIAB) Study indicates that diabetes prevalence in India is progressing rapidly across the nation, reaching a total of 62.4 million persons with diabetes in 2011. The prevalence of diabetes in Tamil Nadu was 10.4 per cent, in Maharashtra it was 8.4 per cent, in Jharkhand, 5.3 per cent, and in terms of percentage, highest in Chandigarh at 13.[6]2 Diabetes is a syndrome in which chronic hyperglycemia leads to long-term damage to various organs including the heart, eyes, kidneys, nerves, and vascular system. Numerous oral changes have also been seen in diabetes patients

The most common oral health problems associated with diabetes are periodontal (gum) disease, salivary gland dysfunction; fungal infections, dental decay and delayed healing; taste impairment, cheilosis, mucosal drying and crack, burning mouth and tongue and alterations in the flora of oral cavity, with greater predominance of Candida albicans, staphylococci and hemolytic streptococci.[3,4] Diabetic individuals also show gingival polyps, enlarged gingiva, abscess formation, periodontitis and loosened teeth.

Long-term diabetic complication	Oral implications
Microvascular disease	Xerostomia
	Greater susceptibility of oral tissues to trauma
	More opportunistic infections (e.g., candidiasis)
	Lichen planus and lichenoid reactions
	Greater accumulation of plaque
	Greater risk of caries
	Delayed wound healing
	Greater susceptibility to periodontal disease
Peripheral neuropathy	Oral paresthesia, including burning mouth or tongue
	Altered taste sensations

(Ref. Rees TD.[5])

Periodontal disease and diabetes- a two way relationship

The first oral complication of diabetes is periodontal disease, which stems from a chronic inflammation caused by various types of bacteria and microbes in the mouths of diabetics. In fact, periodontal disease is frequently referred to as "the sixth complication of diabetes" along with neuropathy, nephropathy, retinopathy, and micro- and macrovascular diseases.[6,7]

The increased susceptibility of periodontal patients with diabetes is due to polymorphonuclear leukocyte deficiencies resulting in impaired chemotaxis, defective phagocytosis or impaired adherence.[4]

Recent data indicate that periodontitis may cause changes in systemic physiology. The interrelationships between periodontitis and diabetes provide an example of systemic disease predisposing to oral infection, and once that infection is established, the oral infection exacerbates systemic disease. These diseases are thought to be associated biologically, and a number of reviews and studies have proposed mechanisms to explain the relationship, including 1) microvascular disease, 2) changes in components of gingival crevicular fluid, 3) changes in collagen metabolism, 4) an altered host response, 5) altered subgingival flora, 6) genetic predisposition, and 7) nonenzymatic glycation.[8]

Accumulation of advanced glycation end products (AGEs) as a result of the chronic hyperglycemic state or diabetes, coupled with the presence of infection and an exaggerated host response, may provide a viable explanation for the clinical outcomes observed in diabetic patients with periodontal disease.[8]

Both animal models and humans suggest that hyperglycemia, in combination with elevations of serum low density lipoproteins and triglycerides, leads to the formation of advanced glycation end products (AGEs) which may alter macrophage phenotype. This may be responsible for dysregulation of macrophage cytokine production and increased inflammatory tissue destruction and alveolar bone loss.(Figure 1)

The primary reparative cell in the periodontium, the fibroblast, does not function properly in high glucose environments. Furthermore, the collagen that is produced by these fibroblasts is susceptible to rapid degradation by matrix metalloproteinase enzymes, the production of which is elevated in diabetes. This results in the cross linking of collagen and AGEs resulting in decreased collagen turnover. So collagen is diabetic patients is aged and more susceptible to breakdown.[9]

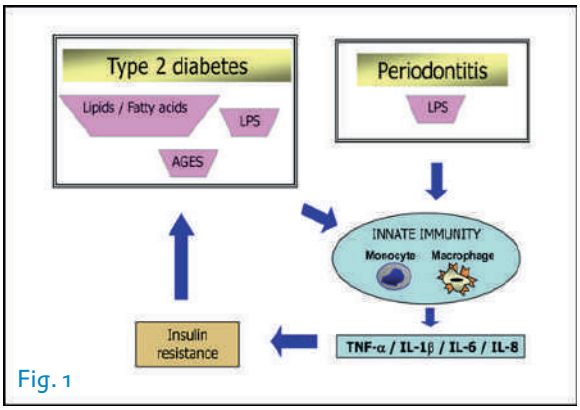

Fig. 1

Periodontitis-induced bacteremia/endotoxemia has been shown to cause elevations of serum proinflammatory cytokines such as interleukin-1 beta (IL-1 beta) and tumor necrosis factor-alpha (TNF-alpha), which have been demonstrated to produce alterations in lipid metabolism leading to hyperlipidemia. These cytokines can produce an insulin resistance syndrome similar to that observed in diabetes and initiate destruction of pancreatic beta cells leading to the development of diabetes. Thus, there is potential for periodontitis to exacerbate diabetes-induced hyperlipidemia, immune cell alterations, and diminished tissue repair capacity. 10 Patients with diabetes show increased incidence of gingival inflammation, gingival polyps, multiple periodontal abscess, enlarged gingiva.(Figure 2

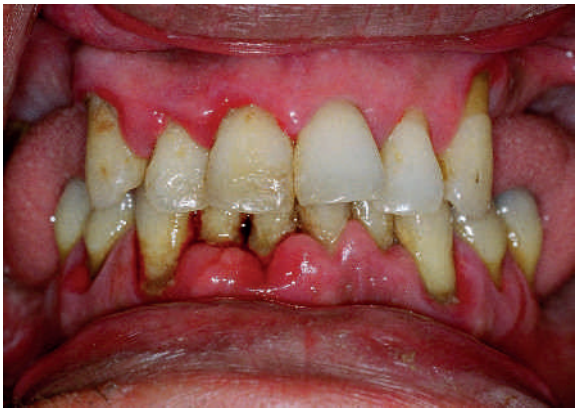
Fig. 2

Xerostomia

Xerostomia, more commonly referred to as dry mouth, is a common complaint among ambulatory diabetic patients associated with the poor salivary flow and with other oral and extraoral symptoms of desiccation. The oral dryness may occur due to disturbances in glycemic control.[11]

The breath of people with diabetes often smells fruity, which may be a result of xerostomia or a change in the thickness of saliva in diabetics. Xerostomia can lead to markedly increased dental caries, parotid gland enlargement, inflammation and fissuring of the lips (cheilitis), inflammation or ulcers of the tongue and buccal mucosa, oral candidiasis, salivary gland infection (sialadenitis), halitosis, and cracking and fissuring of the oral mucosa.[12]

Xerostomia leads to a marked increase in tooth decay.[13] Xerostomia can actually make diabetes worse and that salivatin, a peptide found in human saliva, plays a role in making glucose-stimulated insulin release possible. Salivatin is believed to lower blood sugar after a meal and helps keep blood sugar levels even, a function that appears to be damaged by diabetes.[14] Subjects with type 1 diabetes who had developed neuropathy more often reported symptoms of dry mouth as well as symptoms of decreased salivary flow rates.[15]

Etiology of xerostomia is associated with a non inflammatory, non neoplastic enlargement of the parotid gland believed to occur in 25% of patients with moderate to severe diabetes and especially in patients with type 1 diabetes and poor metabolic control.[16]

Dental caries

Optimum salivary flow rate is responsible for establishing protective environment against dental caries. As xerostomia is observed in diabetes, the individuals are predisposed to the development of dental caries. The relationship between diabetes mellitus and dental caries prevalence is less clear.[17]

Fungal infections

It has generally been assumed that oral candidiasis occurs with increased frequency in patients with diabetes mellitus.[18] Oral candidiasis, a fungal infection in the mouth, appears to occur more frequently among people with diabetes, including those who wear dentures. Diminished salivary flow and an increase in salivary glucose levels create an attractive environment for fungal infections such as thrush.[19] Thrush produces white (or sometimes red) patches in the mouth that may be sore or may become ulcers. It may attack the tongue, causing a painful, burning sensation. It also can cause difficulty in swallowing and compromise your ability to taste.

Burning mouth syndrome

Diabetics are more susceptible to oral infections (including oral thrush) that produce burning mouth sensations. Additionally, diabetics are prone to vascular changes that affect the small blood vessels in the mouth, creating a lower threshold for pain.[20]

Lichen planus

Type I diabetes and Oral Lichen Planus(OLP) are characterized by autoimmune phenomena and T cell immune responses respectively, suggest that the immune system may play a critical role in the appearance of OLP in patients with type I DM. Grinspan's syndrome is a triad comprising of oral lichen planus, diabetes mellitus and hypertenstion.[21]

Conclusion

Blood glucose control is the most important factor in maintaining diabetics' oral health. Rigorous dental hygiene is also imperative for those with diabetes, for without it oral health problems can multiply exponentially. Regular dental checkups and periodontal screenings are important for evaluating overall dental health and for treating dental problems in their initial stages.

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Marijuana: recreation as medicine?

Its psychoactive properties have ensured its extensive use for recreational purposes for the last 5000 years. United Nations has declared it to be the most commonly used illicit drug. But recently the evidence is mounting that Cannabis (marijuana, hashish, bhang) may have medicinal properties. The most recent one comes from Israel. Zach Klein (He has made a documentary "Prescribed Grass" on Cannabis) and his associates of Tel Aviv University treated19 patients with a variety of chronic disorders including terminal cancer, ALS, PSTD etc., with medicinal cannabis. The results were spectacular. Cannabis improved the appetite, relieved the pain and cured insomnia where all other conventional medicines failed. Besides, almost all the patients gained weight and were able to reduce their conventional drug intake. Klein believes the healing powers of Cannabis is nothing short of miraculous. He has urged the governments to change the policy regarding its use.
(http://www.sciencedaily.com/releases/2013/01/130124123453. htm)

- Dr. K. Ramesh Rao

Case Report

Synchronous Presentation of Sporadic Angiomyolipoma and Renal Cell Carcinoma in Contra lateral Kidneys in Patient with no Evidence of Tuberous sclerosis

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Abstract

Angiomyolipoma is an uncommon benign tumor. Clinical presentation of angiomyolipoma either sporadic or in association with tuberous sclerosis has been reported in several studies. Synchronous manifestation of angiomyolipoma and renal cell carcinoma in contralateral kidneys raised clinical suspicion of bilateral renal cell carcinoma in our patient. Patient was a 60 year old male and he was thoroughly investigated for evidence of tuberous sclerosis and was found to have none. Ultrasound evaluation of abdomen did not reveal the characteristic echogenicity of fat in the left kidney. Hence bilateral renal tumors were diagnosed as renal cell carcinoma upstaging the tumor and hence modifying the treatment plan.Computerised Tomography (CT) scan examination further confirmed the diagnosis of bilateral renal cell carcinoma. Histopathology examination however confirmed a sporadic angiomyolipoma in the left kidney and renal cell carcinoma in the right.

Key Words : Angiomyolipoma; Renal cell carcinoma; Synchronous

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Case Report

Angiomyolipoma is an uncommon benign tumor and is composed of adipose tissue,smooth muscle and blood vessels. Renal angiomyolipomas are known to be associated with tuberous sclerosis. But this association occurs only in approximately fifty per cent of cases of angiomyolipomas.[1-5] Tuberous sclerosis was first reported by von Recklinghausen in 1863 and it was described as a syndrome by Bourneville in 1880. It is an autosomal dominant disorder and presents typically with a clinical triad of mental retardation, seizures and adenoma sebaceum.This condition is so named for the potato like nodules present in the brain.[6-9] The revised diagnostic criteria for tuberous sclerosis complex, determined by the Committee of the the National Tuberous Sclerosis Association (now the T.S. Alliance) are the following: Major criteria include facial angiofibromas, forehead plaques, non-traumatic ungual or periungual fibromas, hypomelanotic macules more than three in number and Shagreen's patch; and the minor criteria are multiple randomly distributed pits in dental enamel and gingival fibromas.[9]The clinical presentation of patients having angiomyolipoma with and without tuberous sclerosis has been reported in several studies.[1-4,6-8,10-16] We report a case of angiomyolipoma in one kidney who presented concurrently with renal cell carcinoma in the other kidney, without any stigmata of tuberous sclerosis.

A 60-year-old man presented to the Urology out-patient department with complaints of right flank pain for the past six months and one episode of hematuria. On examination, the patient was conscious, oriented; his vital parameters were normal; no lymph nodes were palpable; a lump was palpable in the right loin; on general and systemic examination, no other abnormality was detected. Routine investigations revealed that the renal functions were normal. Ultrasonogram showed a tumor in the right kidney and it was provisionally diagnosed as renal cell carcinoma. Contrast (Iomeron 400, Iomeprolbracco, Milano) enhanced computed tomogram(CECT) showed a mass lesion in the upper pole of the right kidney which was measuring about 6X5 cm and a mass lesion in the lower pole of the left kidney which was measuring about 3X3 cm (Fig. 2,3). Both the lesions were suspected to be renal cell carcinoma.Partial nephrectomy of the smaller lesion in the left kidney and radical nephrectomy of the larger lesion in the right kidney were planned for. First, partial nephrectomy was done on the left side.It showed a haemorrhagic nodule in the lower pole measuring 3 cm X 2 cm X 2 cm, involving neither the capsule nor the Gerota's fascia. Cut section of the nodule showed solid, ill circumscribed areas of haemorrhage and yellowish areas of fat. Intraoperative, no lymphadenopathy was noted. Histological examination revealed classical

features of angiomyolipoma viz. sheets of mature adipose tissue, tortuous thick walled blood vessels and smooth muscle tissue with areas of haemorrhage (Fig. 1a & Fig. 1b). The tumor cells stained strongly with HMB45 (Fig. 1c) while Smooth muscle actin (SMA) (Fig. 1d) was positive in the blood vessels. After five weeks, radical nephrectomy was done on the right side. A circumscribed mass was seen in the upper pole. The tumor was seen replacing most of the renal parenchyma,involving both cortex and pelvis and bulging outside. The overlying renal capsule, the perinephric pad of fat and the Gerota's fascia were adherent to the tumor at a few foci. But the tumor was not breaching the Gerota's fascia. The tumor showed dark brown areas of hemorrhage, few areas of fat and few areas of necrosis. The preserved renal parenchyma measured 1.5 cm in its maximum dimension. Renal medulla could not be seen grossly. No lymphnodes were seen in the specimen even on meticulous examination.Histology showed renal cell carcinoma – clear cell type – Fuhrman nuclear grade III (Fig.1e). The tumor cells contained intracytoplasmic fat. The renal-capsule, adrenals, the Gerota's fascia, the renal sinus, ureter and the renal vessels were free of tumor.

Discussion

Concurrent presentation of angiomyolipoma and renal cell carcinoma in the absence of tuberous sclerosis has been reported very occasionally.[17] Fifty per cent of renal angiomyolipomas occur in patients with tuberous sclerosis.[14] Coexisting angiomyolipoma and renal cell carcinoma have been described in patients with[6,7,10,12] and without[8,10,12-14,16] tuberous sclerosis. In a review of ten patients with coincidental angiomyolipoma and renal cell carcinoma,50% exhibited tuberous sclerosis.[13] A case who presented with metachronous renal cell carcinoma 9 years after resection of angiomyolipoma in the contra lateral kidney in a patient without tuberous sclerosis has also been reported.[17] The pathogenesis of renal cell carcinoma in a case of angiomyolipoma is still not determined.[7] Possibility of a genetic link between angiomyolipoma and renal cell carcinoma has been suggested with a few molecular studies. Cohen et al described a family in which, out of ten family members, eight had demonstrated association between angiomyolipoma and renal cell carcinoma.[17,18] Genotypic analysis disclosed a reciprocal translocation between chromosomes 3and 8 [t(3;8) / (p14;q24)].[18,19] Matthews et al discuss a case of renal cell carcinoma in a patient without tuberous sclerosis, occurring 9 years after contra lateral resection for angiomyolipoma. Possible predisposition of a patient with angiomyolipoma with or without tuberous sclerosis to develop renal cell carcinoma in the same or contra lateral kidney still needs to be determined. They advocate that any renal angiomyolipoma should be suspected as a premalignant lesion to renal cell carcinoma. Further molecular studies have to be undertaken to determine exactly what makes a patient with angiomyolipoma vulnerable to contract renal cell carcinoma.[16,17] Further,Malone et al state that angiomyolipoma with tuberous sclerosis should be considered suspicious for potentially harboring renal cell carcinoma.[14] The clinical presentation of angiomyolipoma and renal cell carcinoma in patients with tuberous sclerosis is different from that in patients without tuberous sclerosis. Either angiomyolipoma or renal cell carcinoma tends to be multifocal and bilateral in the setting of tuberous sclerosis, whereas both tend to be solitary in non-tuberous sclerosis cases.[8,13,20] Also,tuberous sclerosis patients tend to develop renal failure as compared to the non-tuberous sclerosis patients.[13] Our case presented with right flank pain, an episode of hematuria and no stigmata of tuberous sclerosis complex. A lump was palpable in the right flank but not on the other side. In the recent days, the combined imaging of CT and ultrasonography is being increasingly used to arrive at an accurate pre-operative diagnosis of an angiomyolipoma.[10] The classical findings of an angiomyolipoma are of low attenuation areas of fat on CT and hyperechogenicity on ultrasonography from the multiple fat and non-fat interfaces within the tumor. However, not all angiomyolipomas demonstrate these findings.[2] In our case, ultrasonography could not pick up the lesion in the left kidney though the right kidney lesion was correctly diagnosed as renal cell carcinoma. Further, the echogenicity produced due to the lipid density in case of an angiomyolipoma was not appreciated in this case.CECT picked up both the lesions and diagnosed them to be renal cell carcinomas because the attenuation produced in the left kidney was consistent with that of a carcinoma. It was not too low to render a diagnosis of angiomyolipoma.[8] Grossly, both the lesions had areas of fat and both had extensive areas of hemorrhage.This picture can be seen in both angiomyolipoma and renal cell carcinoma; although fat is less commonly seen in renal cell carcinoma.[5] The radiological diagnosis of an angiomyolipoma would be based on the high fat content present in the tumor. Sometimes it becomes difficult to differentiate between angiomyolipoma and renal cell carcinoma radiologically, particularly if the fat content is less, since the appearance of the non-fat component of angiomyolipoma is similar to renal cell carcinoma on ultrasonogram, computed tomogram and angiographic studies.[13] The high vascularity in case of angiomyolipoma can also mimic carcinoma.[14] The histological type of renal cell carcinoma in this case is the clear cell type and this type has been observed as the most common histologic subtype in both sporadic and tuberous sclerosis – associated cases in a study by Jimenez et al.[12]

Summary

We present an additional sporadic case of angiomyolipoma in one kidney with synchronous renal cell carcinoma in the contra lateral kidney without any signs of tuberous sclerosis. The preoperative diagnosis was renal cell carcinoma on both CT and USG.Nevertheless USG missed to note the lesion on the left side. Partial and radical nephrectomies were performed on the left and right sided kidneys respectively. Histopathology showed angiomyolipoma in the left kidney and clear cell type of renal cell carcinoma in the right kidney.

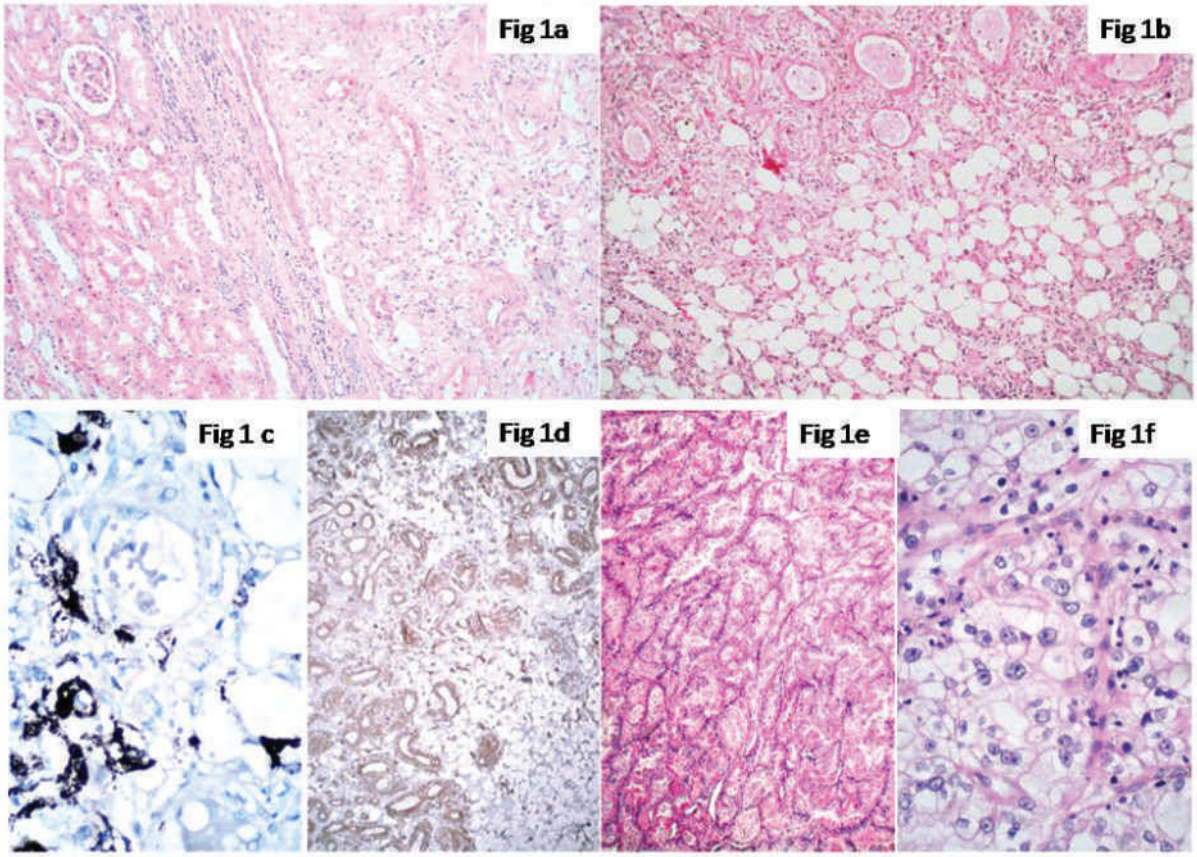

Figure 1a – Section shows angiomyolipoma at the interface with normal kidney, Hematoxylinand Eosin stain, x 50

Figure 1b – Section shows angiomyolipoma with admixture of tumor cells, adipocytes and blood vessels, Hematoxylin and Eosin stain, x 100

Figure 1c – Section shows strong cytoplasmic positivity for HMB-45 in tumor cells, Immunohistochemistry with HMB-45, DAKO Polymer technique DAB Chromogen, x400

Figure 1d – Section shows strong cytoplasmic positivity for Smooth muscle actin (SMA) in blood vessels of angiomyolipoma, Immunohistochemistry with SMA, DAKO Polymer technique DAB chromogen, x100

Figure 1e – Section shows clear cell carcinoma of kidney, Hematoxylin and Eosin stain, x 50

Figure 1f – Section shows Fuhrman nuclear grade III in clear cell type of renal cell carcinoma, Hematoxylin and Eosin stain, x 400

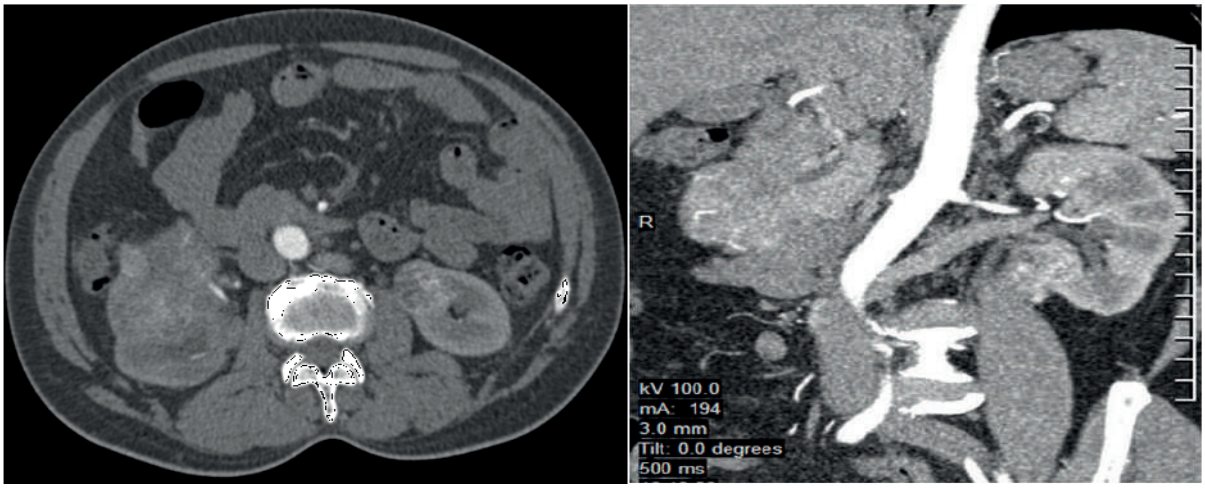

Fig. 2,3 - CECT abdomen showing a mass lesion in the upper pole of right kidney and lower pole of left kidney

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Case Report

Peripheral Giant Cell Granuloma

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Abstract

The peripheral giant cell granuloma (PGCG) is a rare reactive lesion of the gingival tissues. Usual contributing factors include local irritating factors such as plaque, calculus, food impaction, trauma, badly finished fillings and tooth extraction. This case report presents the clinical and histopathological features and management of a PGCG lesion in a 25-year old man.

Key Words : Peripheral giant cell granuloma, Osteoclastoma gaint cell hyperplasia

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Introduction

Peripheral giant cell granuloma (PGCG) is an infrequent exophytic lesion of the oral cavity. It is known by other terms such as giant cell epulis, osteoclastoma, giant cell reparative granuloma, or giant cell hyperplasia. The PGCG can be localized on the attached gingiva or alveolar mucosa. The lesion usually originates from either the periodontal ligament or mucoperiosteum and is more common in the mandibular arch and frequently occurs anterior to the permanent first molars.[1]

It is more common between the fifth and sixth decades of life, with slight predilection for women. The exact etiology of PGCG is unknown, but may be caused by deposits such as plaque and calculus, trauma, rough or overhanging restoration margins, chronic infections, and food impaction. Clinically, the PGCG appears as a bluish red nodular lesion with a smooth, shiny surface and sessile or pedunculated base. The lesion is variable in size, though reportedly rarely exceeding 2 cm in diameter, and are generally soft or rubbery to touch. The lesion is well demarcated from the adjacent tissue. Usually, PGCG is asymptomatic, but the patient may complain of bleeding and pain.[2]

Radiologically, no significant finding can be observed. Rarely, the underlying alveolar bone may show superficial erosion which may present in the radiograph as superficial destruction of the alveolar margin or crest of the interdental bone. Histological features of PGCG reveal a non-capsulated mass of tissue containing a large number of young connective tissue cells and multinucleated giant cells. Hemmorage, hemosiderin, inflammatory cells, and newly formed bone or calcified material may also be seen throughout the cellular connective tissue.[3]

Case Report

A 25-year-old man complaining of pain and swelling in upper right gums was referred to the Dept. of Periodontology, Patient appeared apparently healthy without any significant medical history. On extra-oral examination, patient presented with swelling in the upper right cheek region and involvement of the left submandibular lymphnodes. Intraorally, a dumbbell shaped tumoral mass was present involving the buccal and palatal gingiva of right upper first and second premolars. (Fig.1)

The lesion measured approximately 2 x 1.5 x 1 cm on the buccal aspect and 1 x 10.75 on the palatal aspect.(Fig.2) The patient had noticed the lesion 1 year back and it gradually increased in size. The lesion was well-defined, sessile with a bluish red tinge on the entire surface. On palpation, the lesion was tender, smooth and soft in consistency. An intra-oral periapical radiograph of the involved region showed radiolucency and slight loss in vertical height of the interdental bone. (Fig.3) After thorough clinical and radiological examination, it was decided to do an excisional biopsy of the lesion.

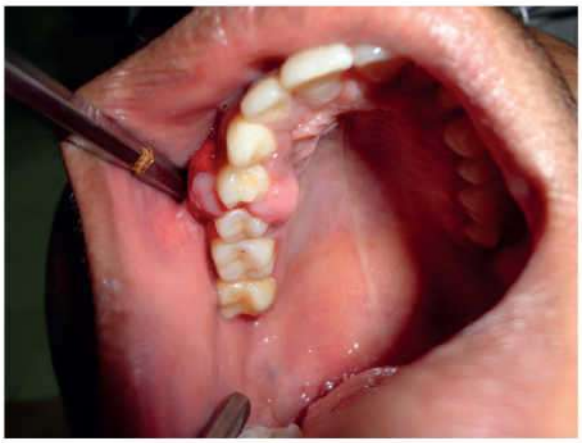
Excision was done with a No. 15 b-P blade by splitting the lesion into buccal and palatal sections. (Fig4, 5, 6) During biopsy, the lesion bled profusely and was controlled by physical pressure. Histopathological examination under low magnification showed proliferative epithelium overlying a vascular connective tissue stroma. Under higher magnification, epithelium was of parakeratinized stratified squamous type. Connective tissue stroma showed numerous proliferating blood vessels with extracellular

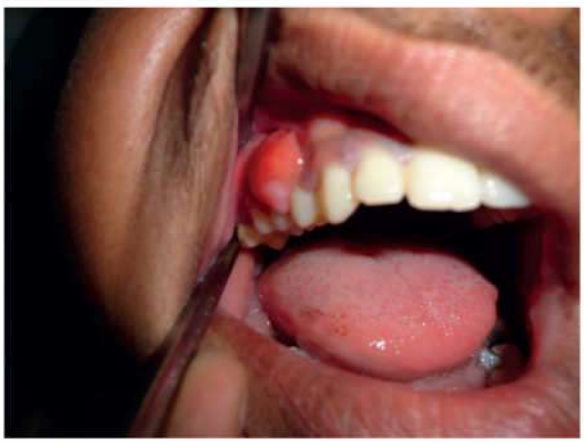
hemorrhage. Several multi-nucleated giant cells were seen interspersed in the connective tissue stroma. (Fig .7)

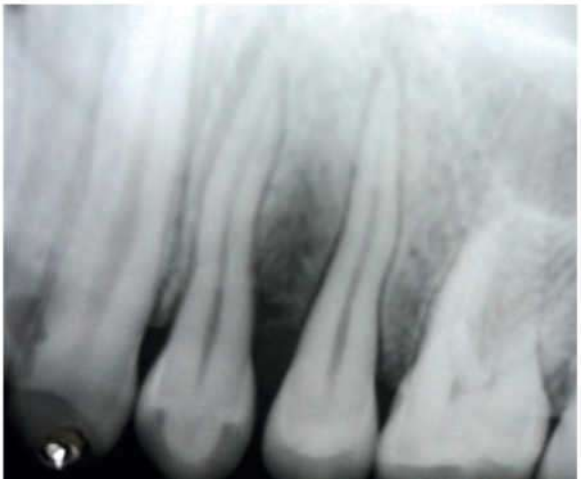
As the lesion was exophytic and hyperplastic in nature, differential diagnosis includes pyogenic granuloma, central giant cell granuloma and fibroma. However, absence of ossification did not support the central giant cell granuloma and presence of vascularity can exclude fibroma. The presence of several giant cells and hemorrhage ruled out other forms of inflammatory hyperplastic lesions such as pyogenic granuloma.

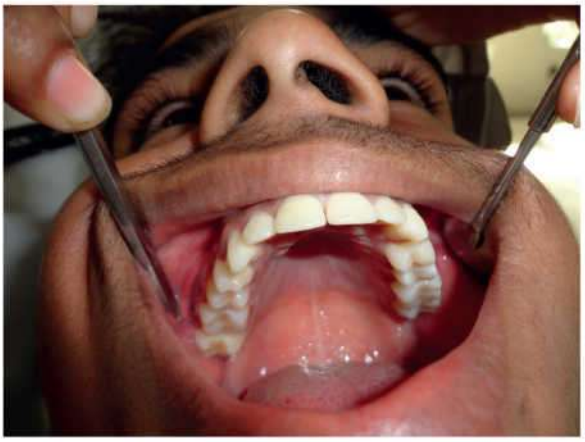
Discussion

Giant cell granulomas (peripheral and central) are benign, non odontogenic, moderately rare tumors of the oral cavity. They originate from the periosteum or









periodontal membrane following local irritation or chronic trauma. Generally, PGCG size varies from 0.5 to 1.5 cm in diameter. There are no pathnogomic clinical features whereby these lesions can be differentiated from other forms of gingival enlargement. Microscopic examination is required for definitive diagnosis. The PGCG has numerous foci of multinuclear giant cells and hemosiderin particles in a connective tissue stroma. Areas of chronic inflammation are scattered throughout the lesion, with acute involvement occurring at the surface. The overlying epithelium is usually hyperplastic, with ulceration at the base.[4]

The exact etiology of PGCG is unknown. Local irritation factors such as poor dental restorations, dental extraction, plaque, and calculus accumulation play significant role in the development of a PGCG.[5] In the above-mentioned case, it could be because of chronic irritation and food impaction. The radiographic examinations generally don't show any findings since it is confined to soft tissue without involving the bone. But in this patient, loss of crestal bone with mild cratering was observed interdentally in the involved region. This may be due to secondary chronic inflammatory changes that might have occurred due to deepening of the gingival sulcus.

Because of the recurrence rate, close follow-up is indicated. The patient was followed upto a period of 6 months with recall visits once every month. Patient had no further complains and no recurrence of the lesion was noted.

The early and precise diagnosis of peripheral giant cell granuloma allows conservative management without risk to the adjacent teeth or bone. Proper therapy and regular follow-up will help in ensuring that there is adequate healing and minimal chance of recurrence, as demonstrated in this case.

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A new role for yellow pigment?

We all recognize bilirubin as the haem-derived pigment that imparts an unpleasant yellow colour to those afflicted with certain liver diseases and haemolytic anaemias. But most people fail to realise that it is not a waste product but a powerful anti-oxidant. In a new study carried out in University of Missouri, the researchers discovered that bilirubin could prevent or limit the extent of vascular damage in individuals at risk for occlusive cardiovascular disease. It does so by inhibiting the growth of vascular smooth muscle cells without killing them. However, as bilirubin is not soluble in water and is rather quickly digested when consumed orally,the challenge is to find a way to exploit this useful property of bilirubin therapeutically to check the largest killer. The authors' suggestion: coat the stents with bilirubin. (Frontiers in Pharmacology, 2012; 3 DOI: 10.3389/fphar.2012.00048)

- Dr. K. Ramesh Rao

From the Pages of History

Great Discoveries – Rabies Vaccination

Dr. R.M.Pitchappan, Research Director, Chettinad Academy of Research and Education, Chennai, India

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Many times' discoveries are accidents. Louis Pasteur was not an exception: he was indeed an average student, skilled at drawing and painting, earned his Bachelor of Arts degree (1840), Bachelor of Science degree (1842) and a doctorate (1847) at the École Normale in Paris, but a careful observer. As most of our researchers learn by trial and error, Louis Pasteur, returning from summer vacation in 1879 to his laboratory in University of Lille, started working on chicken cholera bacilli culture, he had left on the table. The inoculums surprisingly did not produce the disease in the chicken. Something had happened to the culture – presumably the higher summer temperature and drying up of the culture has caused some modification in the bacteria, Pasteur thought. He took another culture from the cellar and that produced the disease in a new bird, but failed to produce the disease in the chicken that was already inoculated with the table left culture – the era of 'attenuation' was born: by growing bacteria in adverse conditions caused 'attenuation'. He reproduced this principle in veterinary anthrax, this time incubating a shallow culture in 42-43 degree celcius, and demonstrated these in a public experiment at Pouilly-le Fort, south of Paris, in the spring of 1881. He used 24 sheeps, 1 goat and 6 cattles; vaccinated animal were all protected against a dose of virulent anthrax bacilli which killed most of the control animals in a few days. This lead to the most dramatic demonstration of all vaccinations, attenuation of Rabies virus by air drying spinal cord of infected rabbits. He was waiting for a chance to test it.

On July 6, 1885, a boy called Joseph Meister bitten by rabid dog was brought to him: Pasteur decided to test his vaccine on this boy. He administered the vaccine and spent sleepless night counting the days: The boy did not develop any classical symptoms of rabies for a month and survived. This success of vaccine brought him immediate fame. An international fund raising campaign to build the Pasteur Institute in Paris was initiated and the Institute was inaugurated on November 14, 1888. Joseph Meister lived the rest of his life, serving as gate keeper at Pasteur Institute Paris.

During my first visit to this great institute, I stood spellbound, emotional to see Joseph Meister's statue, on entering the gate of Pasteur Institute. Though I had taught this history of great discovery for over three decades, every time I travel back in history, admiring these great discoverers and benefactors of Mankind: that is the great power of science that shapes, serves the Mankind and its future.

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Dialogue with the Stalwart

Interview with Dr.R.Venkataswami

Interviewed by Dr. K. Senthil kumar, Department of General Surgery, Assistant Professor, Chettinad Hospital & Research Institute, Kelambakkam, Chennai, India.

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Achievements!!! When the ingredients of success are given in the right proportion, many people tend to achieve…few people struggle their way out and finally achieve even when they are given just the basic requirements…exceptional people do not require anything; they start from scratch and make tremendous, unbelievable achievements! This issue we met one such exceptional person who dared to dream big and devoted his tireless and selfless work not only to make his dreams come true, but also to add another valuable asset to the health care system of our country. Prof. R. Venkataswami started the Plastic Surgery department in Stanley Medical College in 1971 when plastic surgery was just at its infancy in India. In 1973, he started the Hand Injury Service Centre, which was the first in the country. Today, the Institute for Research and Rehabilitation of the Hand and Department of Plastic Surgery in Stanley Medical College is one of the best in the world because of his extraordinary commitment and efficient team. Like great teachers always do, he did not produce students and followers, he produced teachers and leaders who continue to carry the torch all over the country. He is the Founder President of the Indian Society for Reconstructive Microsurgery and the Brachial Plexus Surgery Group of India. He has been invited many a time to deliver lectures throughout the world. He has authored various chapters in renowned text books and has numerous publications in international journals to his credit. He has also innovated quite a few operations in the field of hand surgery. Recognising his academic contributions several awards were given to him.

- He was given the Hon. Fellowship of Royal College of Surgeon Edinburg in the year 1991. (He is the First Plastic Surgeon from this county to get this award).
- He was elected as honorary member of the British Association of Plastic Surgery (Second Indian to be elected).
- He was awarded several prestigious orations and lectures from UK and USA.
- He was given the Hon. DSC from Tamilnadu Medical University.
- He was the visiting professor in Hand Surgery to the world famous Hand Surgery centre in Louistille USA in the year 1998. (First Indian to be Invited)
- Crowning it all was the award of "Pioneer in Hand Surgery at the International level by the International Federation of Hand Societies at its meeting held at Budapest in 2005. (First Indian Plastic Surgeon to get

How did your sixty years of successful medical career begin?

I hail from a small village called Kothaneri near Virudhunagar. My parents were simple rural folk, Gandhian in outlook and very principled. I did my schooling from Ramakrishna Mission Vidyalaya at Perianaikanpalayam Coimbatore, which shaped my character and inculcated in me many values. In fact I came to Madras hoping to join B.A Economics Hons in Loyola College; however it was my destiny that the last date of medical application was postponed and I attended the interview and got selected. The only reason I chose to join Stanley Medical College was because my middle school's Headmaster's name was Stanley. I cannot forget my teacher Mr. Ayyavoo in that school who prepared me to join the Ramakrishna Vidyalayam.

How did you develop interest in plastic surgery?

A. It was Prof.A.S.Ramakrishnan who developed my interest in surgery during my undergraduate days. In 1956, as a final year undergraduate student I listened to a lecture by Sir.Harold Gillies, a world renowned plastic surgeon at Madras Medical College. His pioneering work on reconstructive surgery greatly inspired me. After my post graduation in Surgery from Stanley Medical College, I went to Nagpur to pursue MCh in plastic surgery.

What prompted you to start up a Hand Surgery unit in Government Stanley Hospital in 1974?

The interest in hand trauma was created in me by my guru Prof.C.Balakrishnan at Nagpur. Hand trauma was my thesis for MCh Plastic Surgery. When I returned to Madras there was only one plastic surgery unit in Madras Medical College and so I wished to start a separate unit in Stanley Medical College. The proposal for plastic surgery unit was sanctioned by the government against all odds. Our unit was inaugurated on Jan 26th 1971. The Stanley casualty received more than 3000 cases in 1971. I thought it is a good opportunity to contribute something new and good to the community which was my father's advice. This made me to develop a Hand Injury Service, the first of its kind in the country.

What are the supports you got when you had the new idea? Was the idea received well by the government?

Being the first of its kind in our country, Hand Injury Service was well appreciated by the Government, the Dean and others. What was started as a small department of 20 beds and 18 staff members at Stanley became a National Institute with 80 beds and 107 staff members. This was surely due to the quality of work done by my colleagues.

What were the obstacles you faced?

I had problems getting a ward, adequate staff and equipments. The secret of success is to make the proposal as economic as possible and utilise the available resources to the maximum. The philosophy I practiced was to make the best use of what is available and possible. Your work should speak for you and keep knocking at the doors of the government with your work and I am sure it will be answered positively.

Did you foresee that Stanley Hospital will be one of the World's best hand surgery units with so many referral cases?

No I just started with the idea of doing something new and useful to the society. But it turned out to be one of the leading centres. The credit goes to the entire team.

What did you do to ensure the success of your Hand Injury Service?

I noticed that precious time was lost in shifting the patient from Emergency Department due to unwanted meddling of the wound by the casualty team. This is common in all emergency rooms in all hospitals. To avoid this, a broad red line was painted from the Emergency Department to our Hand Injury Service and the patient was asked to "follow the red line". There, they were immediately received and registered by a 24x7 team and later examined and taken for treatment in a separate emergency theatre carved out of a veranda. Following this they were either admitted or treated as outpatient for full rehabilitation.

How did you develop interest in Reconstructive microsurgery? Can you share with us about the Indian Society for Reconstructive Microsurgery which you started in 1992, you being the Founder President.

In 1976, a renowned plastic surgeon by name Dr. Peter Nathan from USA visited our department and demonstrated small vessel anastomosis with a operating microscope borrowed from the ENT department. I realised that microsurgery was essential in the progress of reconstructive surgery. Soon an operating microscope was obtained. Our first replant was a thumb in 1979 and free tissue transfer in 1981. I felt that a separate forum was required to discuss the various advances in microsurgery and hence I started the Indian Society for Reconstructive Microsurgery in 1992.

Can you share a few words about your teachers and inspirations?

A. I was lucky to have good teachers guiding me all through my career. I can never forget my 6th standard teacher Mr.Ayyavoo who took extraordinary interest in guiding me for higher studies and later in the High school Swami Nishkamananda guided me to go to the Arts College. In Stanley my teacher Prof.A.S.Ramakrishnan who was a man of high ethics and perfection and Prof.C.Balakrishnan who was my teacher in Nagpur where I pursued MCh in Plastic Surgery were great Stalwarts who inspired me to be a good doctor and a surgeon. Every day I remember all of them in my prayers.

How do you look at your students? Are they carrying your thoughts forward?

Yes I am very happy that some of my students like Dr.Balakrishnan, Dr.Sridhar , Dr.Mukunda Reddy and Dr.Rajasapabathy are doing excellently well in their chosen fields. All the above head the various academic associations such as Association of Plastic Surgeon of India, Indian Society for Hand Surgery and Indian Society for Reconstructive Microsurgery.

What is your most memorable moment in life?

It was a great honour to deliver the McIndoe Lecture for 1998 in the Royal College of Surgeons of England. I wish to share one incident of my life. My car which was with me for 20 years refused to start on the last day of my retirement when I had to depart Stanley Medical College, as if even it was not willing to leave the Institute. My assistant drove me home in his vehicle.

How were your college days in Stanley? What does the institution mean to you?

College days in Stanley were wonderful. I was the Student Council Secretary in 1953. I was interested in staging various full length plays. I have acted as Subramaniya Bharathi in connection with AICC session held at Madras. I did my undergraduate and postgraduate studies in Stanley and later chose to work after my MCh Plastic Surgery in my parent institution by organising the Hand and Plastic Surgery Department and I continued for 20 years till my retirement. So Stanley is always close to my heart.

How is your life after the days in Stanley College? How do you engage your time now?

It was never a retirement for me after my service in Stanley. Now I head the Department of Reconstructive Surgery in Apollo First Med Hospital and train DNB graduates. I am involved as a Chairman of Gandhi Niketan Ashram, a welfare institution for the needy in rural India at Kallupatti Madurai District. I spend my leisure to plan and work for them.

You have inspired many generations of medical students. What do you advice the present generation?

The students should have their goals right and work for it with focussed attention. They must follow medical ethics and avoid malpractices. Each one should have a social responsibility and must contribute something useful to the society which made him the doctor.

What are your contributions to the field of Reconstructive surgery?

A. I had great opportunity at Stanley. I had the first Hand Injury Service started in the country in 1974. Similarly I had the first Microsurgical service in the country in 1988. Later I found the Indian Society for Reconstructive Microsurgery in 1992 and Brachial Plexus Surgery Group of India in 2004. I had authored and editored an exclusive hand surgery book published in the year 2008.

Author Index

Subject Index

Thank You reviewers

Chettinad Health City Medical Journal 2012; 1(4): 206 - 206

The success of a journal depends on the authors and the quality of the papers they submit. Equally important is the immense contribution from the peer reviewers. They voluntarily, freely provide their time and expertise to critically evaluate the articles and contribute to their improvement with their valuable comments and suggestions. The following scholars have kindly reviewed the articles for our journal. Chettinad Health City Medical journal gratefully acknowledges their help and support for the journal.

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