Dr.M.Keshav Pai Memorial Oration

PITFALLS IN LINEAR DIABETOLOGY

by

Dr.C.V.Krishnaswami – FRCP(E)., F.A.M.S., D.T.M & H(EDIN)

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- Head of the V.H.S Diabetes Department – Voluntary Health Services, Chennai.
- Formerly Honorary Clinical Professor & Honorary. Physician – Government Stanley Medical College & Hospital, Chennai.
- Chairman – HEALTHTRACK INFO SOLUTIONS PVT. LTD.
Three Thousand Years ago, the ancient Hindu physician Susrutha recognized two types of diabetes – one with its onset in youth and the other due to injudicious diet. These forms are now known as insulin dependent and non-insulin-dependent diabetes. Front cover photograph courtesy of J.J. Hoet, MD.
LETTER TO THE EDITORS

SUSRUTA

I was pleasantly surprised and happy to see the print of Susruta on the cover of the October 1987 issue of the IDF Bulletin (Vol. 32, No. 2). I would like to draw the attention of the editors and readers of the Bulletin to the following facts about this print.

Evidently this photograph, which I obtained from my wife’s leather keychain and have used as a slide, frontispiece, and poster in presentations and publications (notably in August 1982 at the International Symposium on Epidemiology of Diabetes, Sendai, Japan, and in November 1982 at the 11th IDF Congress in Nairobi, Kenya), has reached you after 5 years through Prof. Hoet, whose name has been rightfully acknowledged. But for the sake of esthetic purity—and to set the record straight—I would like to point out that my blockmaker made a slight error when printing this sketch. The sketch used in my publications and on the cover of the Bulletin is actually a mirror image of the original, which depicts Susruta facing our left and using his right hand to grind the pestle (i.e., he was right handed and not a “southpaw” as is seen in these printed versions—my wife still has that leather keychain!).

In any case, I thought that for the sake of accuracy I should highlight these facts and bring them to your attention. I sincerely hope that you will pass this interesting information about the cover print of Susruta on to your readers around the globe.

Dr. C.V. Krishnaswami,
FRCPE, DTM&H(Edin)
Head of the Diabetes Department
Voluntary Health Services
Medical Centre
Madras 600 113, India
Part I

- What is Linear Diabetology?

- Evolution of Diabetes as a specialty and Linear Diabetology as the ‘goal’ for all ills attributed to Diabetes.
Part II

- Diabetes Research Past, Present and Future.
- From Epidemiology to complications
Part III

- Narrative – Based Medicine
  (Illustrative Real time Clinical experience)
Part IV

Conclusions
Part I

❖ What is Linear Diabetology?

❖ Evolution of Diabetes as a specialty and Linear Diabetology as the ‘goal’ for all ills attributed to Diabetes.
PITFALLS OF LINEAR DIABETOLOGY

- Diabetology as a speciality started about 50 years ago.

- Classification of Diabetologists (Prof. Sam.GP Moses)

- Origin of good control of Diabetes vs. Diabetic complications Jean Pirat’s Retrospective analysis. The start of glucocentric tight control as the target for avoiding diabetic complications.

- The next decade; the raise of Diabetologists conclave – IDF – BDA – EASD – ADA – WHO etc.

- The Emergence of sub (super) specialities in Diabetes – Epidemiologists geneticists, Researchers (Experimental Diabetologists), Clinical Diabetologists interested in JOD, MOD, FCPD, GDM (PDG), Diabetic Foot Specialists, General, Ortho & Vascular & Plastic Surgeons, Neuro-Diabetologists, Ophthalm / Retino Diabetologists, Dermo Diabetologists, Behavioural.(Psycho).Diabetologists,.etc.. the list is not complete.
“You are a young graduate. You know every step of the metabolic pathways, every enzyme involved in gluconeogenesis, every detail of the microtubules that lead insulin out of the beta cell. And the more you know about that the less time you have had to talk with patients......today you are starting your medical practice and you have to take care of diabetics (not of diabetes) .......do not trust schemes or classifications too much. After all a patient has a right to be himself regardless of the pattern he should fit into in accordance with your theories.” Jean Pirart 1983.
Comparison of syphilis & DM – Both affect all the systems in the body – know syphilis & you know medicine was replaced by know Diabetes and you know Medicine – with a difference that at this stage the medical industry (diagnostic and therapeutic support (including the nutritionists groups) found out about the tremendous future economic (money spinning) potential of – what by now became the most important ‘disease’ to affect mankind!

The rest is recent history
→ Peter Bennet’s experiments with Pima Indians linking obesity & T2DM. (Arizona USA)
→ Paul zimmet’s global trip with DM starting with Polynesian, Micronesians, Narau Islanders.
→ India the Diabetes capital of the world (WHO)
→ India as the numero uno destination for drug trials – The cancer drug trial flop show (Mayo Clinic & Trivandrum) Rosiglitazone fiasco with McMasters (Canada ) & Chennai.
PITFALLS IN LINEAR DIABETOLOGY

The term Linear Diabetology is coined to denote the Obsessive Compulsive Neurosis (OCN) of both doctors and patients on the Numerical (as against clinical) control of Blood Sugars in otherwise asymptomatic and healthy persons with Diabetes.

The Linear Diabetologist may also be labeled as a Glycaemologist or Blood Sugar Specialist as he/she apparently is utterly keen to bring the blood sugars to “normal” levels by a plethora of drugs and warns (threatens) the patients of the disasters awaiting his body and soul if he/she does not achieve “normal” Blood Sugars & HBA1C values!!

These breed of B.S.S. utterly disregard the normal and Pathophysiologival responses of the human body in health and ill-health and are ready to add on 1,2,3,4 drugs in their effort to subjugate the blood sugar in a Linear manner (their philosophy is simple i.e. 2+2=4 --- perhaps they are unaware of Parkinson’s Law!)

That the human body dynamics & the therapeutic kinetics wage a war in vivo with consequences that are not fully understood and appreciated resulting in the sum total figures (+, −, ×, ÷) of the individual hormonal actions and reactions that are depicted as Blood Sugars, HBA1C, BUN, Serum Creatinine, Electrolytes, etc., is the real key to understanding diabetes control and avoiding the pitfalls of Linear Diabetology.
WHO HAS SEEN A BLOOD SUGAR?

Reflections on Medical education

Frank Davidoff, M.D.

Who has seen the wind?

Neither you nor I;

But when the trees bow down their heads
the wind is passing by.

CHRISTINA ROSSETTI In “who has seen the wind”
The Bharatanatyam Pose captured in this illustration has been described by Dr. Padma Subramaniyam – a renowned dancer and researcher as the “FROZEN MOMENT IN THE WHEEL OF TIME”
Part II

- Diabetes Research Past, Present and Future.
- From Epidemiology to complications
Type – 1 Diabetes Mellitus; Indian & Global Scene – Burdens & Challenges
Incidence of IDDM in children aged under 15
Age-Adjusted Incidence of Diabetes from 1990 to 1996* for Children under 14

- ASIA
  - Kuwait
  - Novosibirsk RUS
  - Israel
  - Hokkaido JPN
  - Chiba JPN
  - Okinawa JPN
  - Hong Kong
  - Karachi PAK

- AUSTRALIA & OCEANIA
  - Canterbury NZL
  - New South Wales AUS
  - Auckland NZL

- NORTH AMERICA
  - Prince Edw Isl CAN
  - Alberta, CAN
  - Jefferson county US

- CENTRAL AMERICA
  - Puerto Rico USA
  - Virgin Islands USA
  - Cuba
  - Barbados, BRD
  - Veracruz MEX

- SOUTH AMERICA
  - Montevideo URY
  - Sao Paulo BRA
  - Cordoba ARG
  - Avellaneda ARG
  - Corrientes ARG
  - Bogotá COL
  - Santiago CHL
  - Paraguay
  - Lima, PER
  - Caracas, VEN

- AFRICA
  - Gafsa TUN
  - Beja TUN
  - Oran ALG
  - Gezira province SDN
  - Monastir TUN
  - Mauritius

*Period varies from one to five years according to data received


The Significance of Certain Epidemiological Variants in the genesis of Juvenile Insulin-Dependent Diabetes Mellitus the need for A Global program of Co-operation.

C.V.KRISHNASWAMI and P.CHANDRA*
Voluntary Health Services Hospital and Government Stanley Hospital, Department of pediatrics, Government Stanley Hospital, Chennai Tamilnadu
APPENDIX (ii)

INDIA
Population: 680 Millions

TAMILNADU
Population: 50 Millions
DIABETES: 2% (1 Million)
JIDDM=0.5% of DM=5000

Prevalence rate = 0.01%
The required sample size of all the ages was 155000 which was obtained from 30 randomly selected corporation divisions of the city. Ten trained social workers recorded required information of the selected families on the prescribed forms by daily house visits.

This study was conducted during 1998 – 1999. Among 156258 individuals of all ages surveyed, there were 60310 persons aged 0-20 years. The age standardized prevalence of known diabetes was 0.02% in those aged < 20 years. This survey indicates that diabetes of any category is not a public health problem in those aged <20 years in Chennai city, India.

Key words: Diabetes mellitus, Type-1 diabetes, Prevalence, Type 2 diabetes, Young population

SERVICES OFFERED BY THE VHS DIABETES DEPARTMENT

In the NGO sector catering to the public of Chennai, Tamil Nadu (India) for over 35 years

The Services Include:

Regular Out-Patient services for all persons with Diabetes

SPECIAL COMPREHENSIVE FREE MEDICARE FOR ALL PERSONS with JIDDM (Type 1 DM with onset below 15 years) includes supply of Insulin, HMBG monitoring/ training with equipment and regular follow up with all investigations like FLOURESCEINE ANGIOGRAPHY for eyes, renal package, foot care etc., treatment of co-morbid conditions, educational and social support, job placements and rehabilitation, plus pregnancy care and delivery.
VHS DIABETES DEPARTMENT

- Diabetes & pregnancy for all with GDM screening
- Diabetes Foot care service
- Diabetes Renal care service
- Diabetes Retinopathy surveillance and prevention of blindness program for type IDDM
- Diabetes nutrition department – clinical services, diploma training and research programmes
- Diabetes specialists nurse educators service and training certificate programme
REHABILITATION SERVICES

- Diabetes Research and academics activities (Shri Prakash CME Programme for doctor).

- Public Education programme (Shri Prakash Endowment Public Lectures).
Peter H. Forsham – M.A., M.D.
Professor of Medicine & Paediatrics; Chief Endocrinologist, Department of Medicine, Director – Metabolic Research Unit, University of California, San Francisco, USA.
Type – 2 Diabetes Mellitus; Indian & Global Scene – Burdens & Challenges

Diabetes Mellitus is the commonest Medical Problem of the 21st Century, affecting the quality of day to day life of over 150 million people of the world cutting across age, gender, racial and economic barriers.
The Story of Epidemiology and Prevention of Diabetes
Prevalence of NIDDM in the age range 30 – 64 Years in Selected Populations
<table>
<thead>
<tr>
<th>Place of Survey</th>
<th>Year</th>
<th>Prevalence of Diabetes</th>
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</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Urban</td>
</tr>
<tr>
<td>ICMAR, INDIA</td>
<td>1972</td>
<td>2.3%</td>
</tr>
<tr>
<td>Multicentre</td>
<td>1979</td>
<td>3.0%</td>
</tr>
<tr>
<td>Daryagunj, New Delhi</td>
<td>1986</td>
<td>9.0%</td>
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<tr>
<td>Kudremukh, India</td>
<td>1988</td>
<td>5.0%</td>
</tr>
<tr>
<td>Eluru</td>
<td>1989</td>
<td>6.1%</td>
</tr>
<tr>
<td>Chennai</td>
<td>1992</td>
<td>8.2%</td>
</tr>
<tr>
<td>Kerela</td>
<td>1999</td>
<td></td>
</tr>
<tr>
<td>Kashmir</td>
<td>2000</td>
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</tbody>
</table>

C S Yagnik, NFI Bulletin, July 1995
Prevalence and Incidence of Type - 2 Diabetes and Impaired Glucose Tolerance in a Selected Indian Urban Population

The I.I.T Study - 1992 - 1993

PV Asha Bai*, CV Krishnaswami**, M Chellamariappan***

RESULTS:

A total of 1198 persons, 455 (38%) females and 743 (62%) males, participated in the study. While 116 (9.7%), suffering from Diabetics were exempted from remaining 1082 (90.3%), 663 (61.3%) males and 490 (38.7%) females, were screened by OGTT.

Department of Diabetes, The VHS Medical Center, TTTI Post, Chennai –600113.

JAPI 1999, VOL 47, NO 11
Conclusions:

1. 64.3% of those with IGT Reverted to normal
2. 30.2% remained status Quo.
3. 5.5% of IGT Diabetes Mellitus
4. The annual incidence Type - 2 Diabetes Mellitus for both sexes was 2.2%

PP.1060 JAPI,1999,Vol. 47, No.11
**Abstract:**

Aim: To determine prevalence of known diabetes in those more than 20 years of age in Chennai city.
Prevalence of Known Diabetes in Chennai – Jointly by The VHS Diabetes Department & The National Institute of Epidemiology, Chennai.

AGE - SPECIFIC PREVELANCE OF KNOWN DIABETES ACCORDING TO SEX

<table>
<thead>
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<th>AGE (YRS)</th>
<th>MALES</th>
<th>FEMALES</th>
<th>TOTAL</th>
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<td></td>
<td>PEOPLE</td>
<td>DIABETES</td>
<td>PREVELANCE</td>
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<tr>
<td>0-9</td>
<td>2066</td>
<td>0</td>
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<tr>
<td>10-14</td>
<td>1267</td>
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<td>20-24</td>
<td>1353</td>
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<td>25-29</td>
<td>1350</td>
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<td>30-34</td>
<td>1168</td>
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<td>908</td>
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<td>818</td>
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<td>389</td>
<td>46</td>
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<tr>
<td>65-69</td>
<td>223</td>
<td>34</td>
<td>15.2</td>
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<td>70+</td>
<td>327</td>
<td>38</td>
<td>11.6</td>
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<tr>
<td>TOTAL</td>
<td>13366</td>
<td>384</td>
<td>2.9</td>
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JAPI, Vol.49, October 2001
The prevalence of known diabetes was low in total population but increased in those aged > 20 and further increased in those aged >= 40 years. The causes for high prevalence in > 40 years age group needs to be explored in this population.

(J Assoc Physician India 2001; 49: 974 - 981).

Conclusion:

The prevalence of known diabetes was low in total population but increased in those aged > 20 and further increased in those aged >= 40 years. The causes for high prevalence in > 40 years age group needs to be explored in this population.

(J Assoc Physician India 2001; 49: 974 - 981).
Epidemiology of Diabetes in India – Three Decades of Research

Netaji Oration, AIPICON, 2005

The landmark studies such as the Diabetes Prevention Programme in USA, the Finnish Diabetes Prevention Programme and the Malmo study have shown the efficacy of lifestyle modification in preventing diabetes in subjects with IGT. A similar prospective study is nearing its conclusion in Chennai which is expected to throw light on the possibility of prevention in the non-obese, insulin resistant Indian population by using lifestyle modification and/or insulin sensitizers.

Studies Showing a rising trend in the Prevalence of Type 2 Diabetes in INDIA.

<table>
<thead>
<tr>
<th>Year</th>
<th>Author</th>
<th>Place</th>
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<th>Urban</th>
<th>Rural</th>
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<td>1971</td>
<td>Tripathy et al</td>
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<td>1972</td>
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<td>1979</td>
<td>Gupta et al</td>
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<td>Murthy et al</td>
<td>Tenali (South)</td>
<td>4.7</td>
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<td>1986</td>
<td>Patel</td>
<td>Bhadran (West)</td>
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<td>1988</td>
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<td>Kudremukh (South)</td>
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<td></td>
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<tr>
<td>1989</td>
<td>Kodali et al</td>
<td>Gangavathi (South)</td>
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<td></td>
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<td>1989</td>
<td>Rao et al</td>
<td>Eluru (South)</td>
<td>1.6</td>
<td></td>
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<td>1991</td>
<td>Ahuja et al</td>
<td>New Delhi (North)</td>
<td>6.7</td>
<td></td>
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<td>1992</td>
<td>Ramachandran et al</td>
<td>Madras (South)</td>
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<td>2.4</td>
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<td>Ramachandran et al</td>
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<td></td>
<td></td>
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<tr>
<td>2000</td>
<td>Ramankutty et al</td>
<td>Kerala (South)</td>
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<td>2.5</td>
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<td>Ramachandran et al</td>
<td>National Urban (DESI)</td>
<td>12.1</td>
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<td>2001</td>
<td>Misra et al</td>
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<td>2002</td>
<td>Mohan et al</td>
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<td>12.1</td>
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<td>2004</td>
<td>Shaukat et al</td>
<td>National</td>
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* Different sample selection criteria

Do epidemiologists cause epidemics?

VOL 341: April 17 1993
The Scandal of Poor Medical Research

We need less research, better research, and research done for the right reasons.

David G. Altman
Medical Statistics laboratory
Imperial Cancer Research Fund
This paper presents the results of computed analysis of 300 randomly sampled cases receiving treatment for MOD in 3 groups: Group A, diet alone; Group B, diet + oral hypoglycaemic agents (OHA), and Group C, diet + insulin. These cases were followed up regularly for 2 years, with periodic assessment of chemical control of diabetes. 32% of the cases were in Group A, 44.3% in Group B and the rest in Group C. 75% of the patients completed the 2-year follow-up. Successful chemical control was obtained in 95% of Group A (P<0.0002) and in 81 + 4.17%(mean) of Group B (P<0.02). Chemical control obtained in Group A was significantly better than in Group B or C. Group A thus acted as an ‘index group’ in the treatment of the cases under study. The skepticism regarding the hypoglycaemic effects of OHA is perhaps because the studies so far published do not have the result in the index group, as obtained in this study. Only such a type of diet could be expected to give sustained good results in the treatment of MOD, when OHA are indicated.
The Story of Biguanides – Phenformin & Metformin

Phenformin

LACTIC ACIDOSIS FOLLOWING PHENFORMIN THERAPY

(A review of authors’ experience in 25 Indian diabetics)

By

C.V. KRISHNASWAMI* and K.VALMIKINATHAN**

It is difficult to make any definite conclusions based on this limited study. At the same time, it is quite speculative that theses rather subtle changes in anion gap are perhaps indicative of the early phase of Phenformin effect. This may well be a physiological adaptation to possibly a type of drug induced stress leading to sodium retention. This possibly has to be entertained in view of the report of Phenformin impairing $NH_4^+$ formation which is quite often implicated in sodium exchange (Rooth and Bandman, 1973).


**Biguanides – Metformin**

We in India have used it for the past 50 years, as did physicians and diabetologists in Europe & U.K.

In 1970s complications were reported with Phenformin like Lactic acidosis and the findings of UGDP study findings that it increased Na, BP and caused fatal stroke, causing premature withdrawal of the drug from the trial – all these brought to the fore Metformin which was claimed to be 10 times less toxic than Phenformin in producing L.A still it took 20 more years for the FDA to allow Metformin into the U.S Market, immediately followed by mega hype on its various beneficial effects.
Contraindications to the use of Metformin

Evidence suggests that it is time to amend the list

Suggested revised contraindications and guidelines for withdrawing Metformin

- Stop if serum concentration of Creatinine is higher than 150 micromols/L. *

- Withdraw during periods of suspected tissue hypoxia (for example, due to myocardial infarction, sepsis).

- Withdraw for three days after contrast medium containing iodine has been given, and start treatment with Metformin only after renal function has been checked.

- Withdraw two days before general anaesthesia and reinstate when renal function is stable.

* Any concentration of Creatinine that is chose as a cut-off point for renal failure will be arbitrary in view of individual patients’ muscle mass and protein turnover, and caution should therefore be used in prescribing Metformin for elderly patients.

BMJ 2003;326:4-5 (4 January)
Cost-Effectiveness of Lifestyle Modification and Metformin Therapy in Preventing Type 2 Diabetes

A three-year study of 3,234 people in the Diabetes Prevention Program (DPP) age 25 or more who had impaired glucose tolerance and fasting glucose levels of 95–125 mg/dl. Participants were randomly assigned to receive placebo, modify their lifestyle (getting 150 minutes of activity per week) and achieve a 7% weight loss, or receive 850 mg of metformin twice a day.

<table>
<thead>
<tr>
<th></th>
<th>Lifestyle</th>
<th>Metformin</th>
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</thead>
<tbody>
<tr>
<td>Delay in development of diabetes*</td>
<td>11 years</td>
<td>3 years</td>
</tr>
<tr>
<td>Reduced incidence of disease*</td>
<td>20%</td>
<td>8%</td>
</tr>
<tr>
<td>Cost</td>
<td>$1,100 (per QALY)</td>
<td>$31,000 (per QALY)</td>
</tr>
</tbody>
</table>

*compared with placebo
QALY (quality-adjusted life year)

The Story of Glitazones – (Thiazolidinediones)

1. **Troglitazone (Resulin):**

   This exciting PPAR Gamma Activator Agent, was approved by the US FDA and began being used clinically in 1997 and after causing **irreparable Liver Damage to Significant number of patients**, was withdrawn from the market in early 2000. The US federal Government Healthcarers are still paying for the treatment of patients with irreversible liver failure caused due to Troglitazone. The story behind the story was what happened in the lower / higher echelons of the US FDA (reported in BMJ / NEMJ).
Diabetes Recall

I often think of the first couple of years after a drug has been approved as its guinea-pig period. After all, even the most careful clinical trials of a new medication usually involve just a few thousand patients. So, in the beginning, only a drug’s most common side effects are known. But once a pharmaceutical is cleared by government regulators, hundreds of thousands, if not millions, of people start taking it. That’s when you get a better idea of the true rate of complications, as well as any untoward interactions with other drugs.

Consider what happened with Rezulin, the diabetes drug that was taken off the market in the U.S. last month. The Food and Drug Administration approved the medication in 1997 after tests on 3,000 people showed that it could control Type 2 (formerly adult-onset) diabetes, which affects 15 million Americans. Although some test subjects developed abnormal liver reactions, no one suffered permanent damage, and no one died. Now that millions have taken Rezulin, however, it has been linked to at least 90 cases of liver failure, 63 of which resulted in death.

When serious complications first started showing up, the FDA strengthened the warning labels on Rezulin and recommended regular liver tests for all patients using it. But not everyone got tested, and it was impossible to predict who would suffer a bad reaction. Then last year the FDA approved two new drugs (Actos and Avandia) that are chemically related to Rezulin but appear to be safer. Rezulin began looking like more trouble than it was worth.

All three drugs work by boosting the body’s response to insulin. Unlike folks with Type 1 diabetes, those with Type 2 usually produce their own insulin. They’re more of a supply-and-demand problem, says Dr. David Nathan, a diabetes expert at Massachusetts General Hospital in Boston. The body can’t keep up with its elevated need for insulin, and it becomes more and more resistant to the insulin it does make. Rezulin was the first drug that directly lowered insulin resistance.

Some critics have argued that the FDA waited too long to ask Warner-Lambert, Rezulin’s manufacturer, to issue a recall. The pharmaceutical company still believes Rezulin is a good drug and blames the media for sensationalizing its risks. But what the people currently taking Rezulin need to know right now is how to get off the drug without jeopardizing their health.

They shouldn’t go cold turkey on their own; their diabetes could slip out of control. And those people who rely on supplemental insulin, many need their doctor to adjust their dose. There are many people who haven’t been put on one of the new alternatives. Doctors rely on several older medications to treat Type 2 diabetes. “I personally have been very cautious about prescribing the new drugs,” Nathan says. Besides, Actos and Avandia also require precautionary liver tests.

It may be possible to beat insulin resistance through lifestyle changes. Losing weight, if you’re overweight, is a start. But even for those who have trouble dropping kilos, getting more exercise and adding whole grains to your diet can lower your resistance and decrease your need for medication. No one ever said treating diabetes is easy, but there is a lot people can do to keep it from controlling your life.

—By Christine Gorman

For more information on Rezulin or diabetes, visit time.com/personal. You can e-mail Christine at gorman@time.com

GOOD NEWS

PAINFREER THINGS

Say goodbye to pain and suffering.

PAINRELIEVER

A drug that works like magic.

MOTHER LOAD

When Mom’s blue, the kids feel it.

Hidden Herpes

Thank you, don’t have it.

The answer is a blood test.

Dr. L.的位置

Shame.

MM Celebes

Your doctor calls it: Blood tests. -- Ms.

NOT JUST FOR DOGS

Finally, a broad look at whether glucosamine and chondroitin—two wildly popular arthritis treatments—do any good.

BAD NEWS

MOTHER LOAD

When Mom’s blue, the kids feel it.

Hidden Herpes

Thank you, don’t have it.

The answer is a blood test.
City Institute to take part in diabetes prevention project

The six-year project - Diabetes Reduction Assessment with the drugs, Ramipril and Rosiglitazone, is in coordination with the McMaster University, Canada, with partial funding of the Canadian Government.
The wonder drug that wasn’t

By C.V. Krishnaswami

Diabetes mellitus (the adult-type or Type 2) is indeed common in our country with an age-standardised prevalence of about: 2.53 per cent for all ages; 0.62 per cent for 0-20 years; 4.16 per cent for those over 20 years; and 9.25 per cent for those above 40 years and above, as was revealed in a study conducted by our department in collaboration with the National Institute of Epidemiology.

I would like to say that this would mean that there are about four per cent of the population above the age of 20 years and nine per cent of those above 40 years would have known diabetes. In this population, if tested by the oral glucose tolerance test, we could diagnose impaired glucose tolerance (IGT) which is borderline diabetes, in a high percentage of persons (up to 25 per cent as was shown in a study conducted by our department on the IIT campus for two years and published in the Journal of Association of Physicians of India, November 1999).

The study also showed that after one year of follow up of these IGT cases, with monthly counselling by our team on diet, exercise, and lifestyle modifications, 64.3 per cent of these cases reverted to normal without resorting to any drug therapy and 30.2 per cent remained status quo, while 5.5 per cent of the IGT cases progressed to frank diabetic state.

The important questions therefore are:

(a) whether drug intervention is prima facie justified in trying to postpone or prevent the possible progression of this small percentage of IGT cases (i.e. for the questionable benefit of five per cent we have to treat all the 100 per cent.

(b) whether these drugs used over the six-year period of study planned by a Canadian agency are safe and without serious side effects? I would like to draw the attention of all diabetologists and the public to the report in the Time magazine (April 17, 2000) titled ‘Diabetes Recall’ (page 50). The drug in question which was approved rather hastily by the FDA in January 1997, was Rezulin or Troglitazone and was withdrawn in March 2000 on account of causing irreversible liver damage in an unacceptable large number of people treated with this; also there are some reports regarding the role of the drug company in playing down the potentially fatal risks associated with Troglitazone during the approval process.

OPINION

by the FDA in the U.S. (British Medical Journal, March 24, 2000).

(c) The drug Rosiglitazone, that is being planned to be used in the diabetes prevention trial by three well-known institutes — Madras Diabetes Research Foundation, Chennai; St. John’s Medical College and M.S. Ramaiah Medical College (both in Bangalore) — in collaboration with the McMaster University, Canada, for a six-year period, is a modification of Troglitazone which has been withdrawn. It has to be used with great caution particularly in Indian subjects who are prone to a variety of liver ailments including due to nutritional, viral, amoebic and various other causes not to mention alcohol abuse and its effects.

Dr. David Nathan, a top diabetologist from Boston is quoted as saying: “I have been very cautious about prescribing the new drugs”. He was referring to Rosiglitazone and its sister drug Pioglitazone. Besides both these require regular monitoring of liver functions. While these groups of drugs require careful monitoring by experts even in the treatment of full-fledged diabetics, it looks rather dangerous to embark on a long-term study on human subjects (with borderline diabetic curve and no symptoms) without adequate knowledge (or evidence of its long term ill effects on the liver).

(d) Our study has shown that 95 per cent of the IGT cases do not progress to frank diabetic state if properly counselled and they do not require any drug therapy; this percentage could be increase even more if diabetes educational inputs (using modern methods such as the Internet Postal in various languages) are made available to the people all over the country. As such I feel constrained to question the ethical/moral propriety of drug intervention for over a six-year period, using compounds whose long-term track record is not yet known fully, and the predecessor drug of the same group was withdrawn after usage for only three years with documented irreversible liver failure cases.

The other question, to be asked is, whenever such drug trials are conducted with international agencies, whether these are done after obtaining approval from a suitable Government committee as it involves public health and welfare.

Also to be taken into account are the funding agencies and their competing interest in the project.

Lastly why does a drug trial planned for the next six years need so much publicity in the ‘lay press’ even before the start, if the results are to be unbiased?

The second drug Ramipril mentioned in the study is an expensive cardioprotective agent and to use this over many years on borderline asymptomatic IGT patients for possible prevention or postponement of ‘diabetes’ would certainly not benefit the patient, but probably ringing in millions of dollars to the manufacturer’s kitty.

(The writer is Head, Diabetes Department, VIMS Medical Centre, Chennai.)
Diabetes drug with little side-effects

Dr. V. Mohan, Director, Madras Diabetes Research Foundation, Chennai, and Dr. Salim Yusuf, Director, Division of Cardiology, and Dr. Hertz Gerstein, Director, Division of Endocrinology, McMaster University, Hamilton, Canada, write:

This is in response to the news item “The wonder drug that wasn’t (The Hindu, July 5)” to set the record straight.

The Diabetes Reduction Assessment with Rosiglitazone and Ramipril Medication (DREAM) is an international study which has undergone extensive peer reviews by several international bodies including the Canadian Institutes for Health Research and other scientists in the U.S., the U.K., Australia, and several European and South American countries. The trial has been approved by the Food and Drug Administration (FDA) in the U.S. and the Health Protection Branch of Health Canada for conduct in these countries. Thus the DREAM study has received extensive scrutiny, review and approval.

Dr. C. V. Krishnaswami of the VHS Medical Centre, Chennai, has unfortunately extrapolated the side-effects of Troglitazone to a different compound that we are using in the trial, namely Rosiglitazone. It is indeed true that Troglitazone was banned due to liver toxicity. But precisely for this reason, Rosiglitazone an Pioglitazone the next generation drugs of this new class of insulin sensitizers have been very carefully and extensively evaluated in clinical trials across the world to ensure their safety and efficacy. Rosiglitazone is now available worldwide and till date there have been no reports of liver toxicity with this drug although several million prescriptions have been dispensed. In India, several drug trials were conducted before the drug was marketed. It has been the experience of diabetologists all over India that many patients whose diabetes could never be controlled well are now maintaining excellent control after addition of this drug. Until now, there has not been any report of liver toxicity due to this drug in India although several thousand patients are using the drug. The only side-effects reported are weight gain and mild swelling of feet in some patients both of which are dose related and reversible if the drug is withdrawn. Rosiglitazone, and the insulin sensitizers in general, address the core defect in diabetes, namely insulin resistance; and hence it makes sound physiological sense to use these drugs early in the course of the disease, namely at the stage of impaired glucose tolerance to try to prevent diabetes. The DREAM study is an attempt in this direction.

Ramipril prevented strokes

Regarding the other drug, Ramipril, Dr. Krishnaswami is right in saying that it is primarily an anti-hypertensive agent and his comments were probably justified before the HOPE trial. But in the light of the landmark HOPE trial which showed that Ramipril actually prevented diabetes (although it was not an expected end-point of that trial), the DREAM study assumes great significance. It is well-known that subjects with impaired glucose tolerance (inability to handle a glucose load appropriately, but no diabetes) are at the same risk of developing cardiovascular complications as subjects with diabetes. In the HOPE study, Ramipril prevented heart attacks, strokes and cardiovascular-related deaths in both diabetics and non-diabetics with previous cardiovascular disease. Thus, irrespective of whether Ramipril prevents diabetes or not, it could definitely be expected to reduce cardiovascular morbidity and mortality in the study particularly since IGT subjects are known to have significantly higher prevalence of hypertension. If the study eventually proves that by using one drug one can prevent diabetes, control BP and reduce cardiovascular morbidity and mortality, it would indeed be a “DREAM” come true.

It is a tribute to India that for such a landmark study, Indian diabetologists have also been invited to take part. Whenever a new trial is taken up, it tries to answer unsolved questions and thus improve the lives of patients. Dr. Krishnaswami himself states that 5.5 per cent of IGT developed diabetes every year in his study.

A simple calculation will reveal that this works over to 55 per cent conversion to diabetes over a 10-year period. In fact, several studies now suggest that Indians with IGT probably develop diabetes at a faster rate than other ethnic groups. Given the millions of people at risk of developing diabetes in India, nowhere are prevention studies more relevant than in India.

Needless to say, the study will have to be reviewed and approved by the Ethical Committees of all three institutions participating in the trial and all necessary regulatory permissions will have to be obtained before it is implemented in India. Further, an independent International Data and Safety Monitoring Committee consisting of eminent scientists and physicians will carefully monitor all aspects of the study. This provides a high level of oversight and protection for the participants in the study.

No progress can be made in the field of medicine without trying out newer methods of treatment. In this case, the study does not involve any experimental drugs but is merely an extension of the use of two well-established drugs for a new indication — to try to prevent diabetes itself. If, at the end of the study, we have been able to prevent diabetes and/or prevent cardiovascular morbidity and mortality, we would consider our efforts to have been worthwhile.
Issues concerning ‘wonder drug’

Dr. C.V. Krishnaswami, Head of the Diabetes Department, Voluntary Health Services (VHS), Chennai, writes:

On July 1, The Hindu published a news item ‘City institute to take part in diabetes prevention project’ (Chennai city edition Page 3). It raised some important questions relating to the ethical and medical aspects of drug intervention studies in the prevention of a symptomatic impaired glucose tolerance stage of diabetes and the need to monitor these by an independent body of experts, familiar with our people. ‘The National Academy of Medical Sciences’ (which is a constitutionally-created apex body of medical scientists) is one such. My viewpoint was published unabridged by The Hindu on July 5, under the title ‘The wonder drug that wasn’t’ (Page 11). In my write-up I had not mentioned the names of any person or institution.

After a gestation of three weeks, Dr. V. Mohan, Director, Madras Diabetes Research Foundation, Chennai, and Dr. Salim Yusuf, Director, Division of Cardiology, and Dr. Hertz Gerstein, Director, Division of Endocrinology, McMaster University, Hamilton, Canada, presented their viewpoint “to set the record straight”. This was published in The Hindu on July 26 (Page 13), where my name was repeatedly mentioned. I do not wish to enter into an argument, at any personal or institutional level, on what has been said by them. But the three writers have not answered any of the following points:

1. The medico-moral issue of using chemical compounds on a long-term basis for a long number of years on symptom-free individuals with borderline glucose tolerance (IGT) test abnormality in laboratory tests; (2) Drugs that have been in clinical use on patients for about three years in a study spanning for more than six years; (3) The medical wisdom in the choice of the drugs; (4) The use of statistics to create panic in the minds of the public is to be abhorred. I had quoted a study where 5.5 per cent IGT cases became diabetic in the one-year study period, and also noted that 64.3 per cent of the same group which had IGT became normal and 30.2 per cent remained status quo, during the same period.

To extend this number unilaterally to the diabetes conversion alone with simple arithmetical jugglery is not scientific and contrary to medical statistical principles; (5) There is a need for an autonomous statutory national committee of experts — e.g., the ethics committee of the National Academy of Medical Sciences — to clear such drug trials affecting the lives of a large number of people; and (6) and the funding agencies involved and their competing interests.

I have been in clinical practice of diabetes, research and education for three-and-a-half decade and fully support progressive initiatives in clinical research in diabetes. At the same time, the medical profession should bear in mind the oath of Hippocrates that we should do no harm to patients by our actions.

I would leave it to the medical intelligentsia and the enlightened readers of The Hindu to decide whether the points raised by me have been answered by the three medical men. Generally, people live on, because of the hope and dreams, and sometimes in spite of them!
The Story of Glitazones – (Rosiglitazone)

“Rosiglitazone – Useful Drug but has Side Effects”

<table>
<thead>
<tr>
<th></th>
<th>Before Treatment</th>
<th>After Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mean total cholesterol</strong></td>
<td>188 + 37</td>
<td>212 + 41</td>
</tr>
<tr>
<td><strong>Mean LDL cholesterol</strong></td>
<td>108 + 30</td>
<td>126 + 38</td>
</tr>
<tr>
<td><strong>Mean Triglycerides</strong></td>
<td>201 + 94</td>
<td>228 + 108</td>
</tr>
<tr>
<td><strong>Mean HDL/LDL ratio</strong></td>
<td>4.6 + 1.0</td>
<td>5.3 + 1.2</td>
</tr>
<tr>
<td><strong>Mean HDL</strong></td>
<td>42 + 10</td>
<td>41 + 8</td>
</tr>
</tbody>
</table>

The weight gain and adverse lipid profile are probably secondary to the PPAR gamma activation. These receptors are highly expressed in the adipocytes and lead to excess adipose tissue deposition. In addition, activation of PPAR gamma increases transcription of certain insulin sensitive genes influencing adipocyte differentiation and function.

This results in changes in fat by 10% but increases subcutaneous fat 20-30% with an overall increase in fat by 10%. This is referred to as the thiazolidinedione paradox as despite overall increase in fat insulin sensitivity markedly improves because of its effects on the visceral fat. These side effects must be looked for in all patients on Rosiglitazone. Newer thiazolidinedione compounds with favorable effects on lipid profile and no other side effects are the urgent need of the hour.

S.Vidya, V.Mohan – MV Diabetes Specialities Centre and Madras Diabetes Research Foundation,

#35, Conran Smith Road, Gopalapuram, Chennai – 600 086, India.

JAPI Vol 50, April 2002
Rosiglitazone: Increased Risk of Heart Attacks

It has now been established that the use of rosiglitazone, as compared to other agents, for the treatment of Type 2 diabetes is associated with significant increase in the risk of myocardial infarction and risk of death from cardiovascular causes. The conclusions are based on meta-analysis of 42 randomized, comparator trials involving 27,843 patients.

The mechanism for the increased risk may be due to adverse effect of rosiglitazone on lipids, particularly increase in low density lipoprotein (LDL) by 18.6 per cent. Other factors could be the drug’s propensity to precipitate congestive cardiac failure and reduction in haemoglobin levels that can lead to myocardial ischaemia.
Pioglitazone Falls Short of Promise –
Drug’s benefit – to – risk ratio Unclear
by
Joel R. Cooper, Health Behaviour News Service

DOC News, December 2006 (ADA)
PROactive Results
Overstated and Misleading

Pioglitazone investigators ignore unfavorable findings while highlighting "principal secondary end point" outcomes

By Jay S. Skyler, MD

There were 58 fewer primary end points (57 fewer principal secondary end points) with pioglitazone, but "from the patient's perspective, is it better to have healthy arteries in the heart than a failing heart?" she writes, pointing out that the prognosis of heart failure is particularly poor in patients with type 2 diabetes.

The PROactive investigators conclude, "in patients with type 2 diabetes who are at high cardiovascular risk, pioglitazone improves cardiovascular outcome, and reduces the need for tegmental placebo," and "we believe our results are generalizable to all patients with type 2 diabetes." I For the reasons reviewed above, as a disciplined clinical trialist, I would argue that such conclusions statistically and clinically are not justified and make a mockery of our system of evidence-based medicine. To me, this is a sad tale.

Jay S. Skyler, MD, is a professor in the division of endocrinology, diabetes, and metabolism at the University of Miami and program director of the General Clinical Research Center.
## The Story of Oral Hypoglycaemic Agents

<table>
<thead>
<tr>
<th>Insulin Secretagogue (sulfonylurea or shorter-acting meglitinide)</th>
<th>Metformin</th>
<th>α- Glucosidase Inhibitor</th>
<th>Thiazolidinedione</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sulfonylureas contraindicated in severe liver/renal disease. Meglitinides useful for postprandial hyperglycemia or hypoglycemia with sulfonylureas Nateglinide safe with liver/renal disease.</td>
<td>If obese, Renal/liver function normal. No acute illness, GI disease, CHF, or alcohol abuse. Cr &lt; 1.4 (women) Cr &lt; 1.5 (men) Hold if IV contrast dye procedure &gt;= 80 yr if renal function not reduced.</td>
<td>Milder presentation. If postprandial hyperglycemia is predominant pattern. No GI disease.</td>
<td>Abdominal obesity, additional signs of metabolic syndrome (insulin resistance, hypertension, and dyslipidemias). LFT, normal, monitor at baseline, every 2 mo for 1st yr, and periodically thereafter. No hepatic impairment. No NYHA Class III or IV CHF. If edema, lower dose and/or add diuretic. Safe with renal disease.</td>
</tr>
</tbody>
</table>
Diabetes Drugs Don’t Boost Beta-Cell Function

“We did not find any evidence that either pioglitazone or metformin improved beta-cell function,” researchers conclude.


April 2007 DOCNEWS
Estimated number (in millions) of people with diabetes, worldwide:

- 1985: 30 million
- 1995: 135 million
- 2003: 194 million
- 2025: 330 million

Increase in deaths from diabetes over next 10 years:

- India — 35%
- the Americas — 80%
- the western Pacific and eastern Mediterranean regions — 50%
- Africa — >40%

UNIVERSITY GROUP DIABETES PROGRAMME (UGDP 1961 TO 1970)

This landmark multicentric clinical trail was designed elaborately by the high priests in academic institutions across the length and breadth of the USA and studied 823 diabetic patients for 9 years; the full report of the study was published in 1970\(^4\)

The salient points to note are:

a. Biguanide drug (Phenformin) was dropped from the trail during the 6\(^{th}\) year on account of significant increase in hypertension and cerebrovascular stoke observed in this treatment group.

b. Sulfonylurea (Tolbutamide) group was found to have more cardiovascular morbidity! mortality than the Insulin or placebo (no drug) group.

A hue and furore on the Pros and cons of the UGDP findings followed for the next one year with about 100 protagonists and over 150 antagonists publishing their findings. A consensus process followed and all diabetologists agreed that the trial was not fool proof and hence continued use of sulfonylurea drugs were thought to be safe provided they were used according to specified guidelines, following the failure of Diet and Exercise in controlling cases of NIDDM. (ADA Policy Paper, 1979)\(^5\).
This study of NIDDM (type 2 diabetes) with 23 centres recruiting 5102 patients with newly diagnosed type 2 DM involved different modalities of treatment with a follow-up period of nearly 14 years. The cost of the study, difficult to calculate, but conservatively estimated to be several billions of pounds. The findings revealed again what was well known from the times of Jean Pirat (over 30 years ago) that tight control of diabetes sharply reduces risk of blindness, kindly failure and more importantly heart disease; also tighter control of blood pressure along with diabetes reduced the risk of strokes, and other diabetes related deaths also by a third\(^8\).

The UKPDS also throws up important bomb-shells.

a. More patients treated with chlorpropamamide developed high B.R and hence it was withdrawn from the study.

b. In a randomized sub study, the addition of Metformin to the existing sulfonylurea drug, and intention-to-treat analysis showed that the group assigned to combined Metformin / sulfonylurea therapy had a 96% increase in diabetes-related deaths and a 60% increase in all cause deaths compared with the patients assigned to continue maximal dose of sulfonylurea drugs alone\(^9\).

What is the outcome of these findings in clinical practice? There is a sharp resurgence and upward trend in the usage of Metformin and sulfonylurea / Metformin combinations in the world led by the USA! Truly the human brain and its behavior is the most baffling thing to fathom on this plant earth!!.
Shame: the elephant in the room
Managing shame is important for improving health care

Frank Davidoff – USA.

In 1960’s the results of UGDP showed that Tolbutamide, was associated with a significant increase in mortality in patients who developed Myocardial Infarction. The obvious response from Medical Profession should have been gratitude: here was an important way to improve the safety of Clinical Practice. But in fact the response was doubt, outrage, even legal proceedings against the investigators; the controversy went on for years. Why?
## STATINS & SUNLIGHT

<table>
<thead>
<tr>
<th>STATINS</th>
<th>SUNLIGHT</th>
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<tbody>
<tr>
<td>SIMVA</td>
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<td>PRAVA</td>
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<td>LOVA</td>
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<td>ATORVA</td>
<td></td>
</tr>
<tr>
<td>ROSUVA</td>
<td></td>
</tr>
<tr>
<td><strong>S+FIBRATE (PPAR (\cong) AGENT)</strong></td>
<td></td>
</tr>
<tr>
<td><strong>S+EZETIMIBE</strong></td>
<td></td>
</tr>
<tr>
<td>S+cachannel blocker(AMLODEPINE)</td>
<td></td>
</tr>
<tr>
<td><strong>S+ASPIRIN</strong></td>
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</table>
This 86 year old lady a pavement dweller & destitute has never taken a Statin in her life!!!

"The low-minded are happier than men who know goodness, for they are never troubled by the pangs of conscience."

_Thirukkural – Kural 1072._
Rosuvastatin: Risky in Indians

As Per data submitted to the U. S. Food and Drug Administration (USFDA). The pharmacokinetic behavior of rosvastatin is ethnic-sensitive with blood levels reaching higher levels in Asian populations compared to Caucasians. This can lead to more severe side effects such as life-threatening rhabdomyolysis. Because of these findings, the innovator Company has been asked to generate more data on Asians.

Western drug regulators have made it obligatory that prescribers inform all patients that rosvastatin can cause muscle injury which in severe cases “Can cause kidney damage and other organ failure that are potentially life-threatening.” Hence patients should “promptly report signs and symptoms of muscle pain and weakness, malaise, fever, dark urine, nausea or vomiting” to their doctors.
Prof. CVK with the Legendary Late Prof. Max Ellenberg of Mt. Sinai Hospital, USA, fondly called as the Father of Diabetic Neuropathy.
Flow – chart for management of Foot Infections in DM.

Figure 6.1 Flow chart outlining the current approach in the management of the diabetic foot with ulceration/infection. Reproduced with permission from www.diabetopaedia.com
Trophic ulcer right big toe with gigantism due to AV shunting in diabetic foot

Digital gangrene due to infection in diabetic foot. Note the fullness and pus in the arch of the foot
Decompression surgery done at the right time saves the limb from amputation.

The route of spread of infection in the diabetic foot.
Infection & Disarticulation of toe. Infection persisting with upward spread, systemic toxaemia, hypoglycemia & hyperpyrexia.

Charcot's changes with distortion of the digits - Advanced condition with bony involvement in the diabetic foot.
Big toe with part of it missing

Doppler study showing AV shunting in the diabetic foot and the fast forward flow
Swollen foot with bleb

Ulcer dorsum of foot
International Consensus on the Diabetic Foot

by the International Working Group on the Diabetic Foot
Changes in chronic wound management: perspectives from Tamil Nadu, India

C. V. Krishnaswami, N. S. Raji, K. M. Ramakrishnan and M. Babu

INTRODUCTION

Susruta (1000 BC), the great Hindu teacher and surgeon in India, introduced the concept of cosmetic surgery by reconstructing a chopped nose using a skin flap from the cheek. Wound healing was practiced by the Ayurvedic physicians (using the system of Indian medicine) starting from Charaka (500 BC); they used various herbal and plant products to accelerate healing of chronic wounds, mostly traumatic or surgical wounds. There are records of the usage of the powder of Sappan-wood, liquorica, barberly plant and cotton soaked in sesame oil. Susruta's Samhita (compendium) mentions the use of black ants for suturing.

The aim of this chapter is to introduce some of the common denominators as well as changes related to chronic wound management in Chennai, Tamil Nadu, a south-eastern state in India.

DEFINITION AND NATURAL HISTORY

A wound is a break in the continuity of skin or mucous membrane. Wounds must be treated as individual entities since they may be acute or chronic, have different etiologies, be differently located or they may be infected.

The healing process will be adversely influenced by comorbid conditions, systemic deficiencies and environmental (external) factors. Proper wound treatment requires knowledge both of the normal healing process and of the various factors influencing it. Treatment is often based on tradition and experience, though it ought to be evidence-based. It is difficult in India as elsewhere to adopt such an approach without local evidence. This chapter illustrates some evidence that could be influential in changing local concepts towards wound management.

The basic aspects of wound healing are similar in soft tissues. Continuity and strength are restored by formation of connective tissue and by epithelial overgrowth forming a fibrous scar. This is a continuous process, which for simplicity can be divided into three phases. The first phase is inflammation, also sometimes referred to as the lag phase; the second phase is proliferation, also sometimes referred to as the phase of fibroplasia; and the third phase is maturation.

The immediate response to wounding is vascular (briefly: initial vasoconstriction followed by vasodilatation, changes in capillary blood flow and permeability).
Figure 6.2 A 45-year-old woman from Singapore, a known diabetic for 14 years, NIDDM with polyneuropathy (diminished ankle jerks), preserved sensations of pain, vibration, heat and cold, full foot pulses present bilaterally, presented with a large 6.0 x 4.5 cm non-infected chronic ulcer and hypertrophied edges of more than 2 years’ duration and failed skin grafting twice.

Figure 6.3 The same patient as in Figure 6.2 was treated with pulsed galvanic stimulation using silver-mesh stocking electrodes for 4–6 h daily in an outpatient setting.

Figure 6.4 After 4 months, the ulcer in Figures 6.2 and 6.3 reduced in size from 6.5 cm to 2.5 cm.

Figure 6.5 A 55-year-old female NIDDM (but presently insulin-requiring) patient had a severe degree of sensorimotor polyneuropathy and classical diabetic foot. She presented with acute thermal injury to the lateral three toes of the right foot (dorsal aspect). After 2 weeks of dressings and medication, skin grafting was considered to accelerate healing. This was unsuitable as she had cardiomypathy and other problems. She did not want to undergo anesthesia and opted for the alternative modality of therapy. She responded well to daily application of the silver-mesh stocking electrodes with pulsed galvanic stimulation to the affected foot. The bluish coloration of the third digit at presentation improved in color with 1 week’s therapy and the entire dorsal ulcers, which had exposed the tendons, epithelialized within 4–6 weeks.
Diabetes detected prior to pregnancy (Group I)
Diabetes detected during pregnancy (Group II to Group IV)
(or) Gestational diabetes mellitus

GDM - myth or reality?

Is it necessary and worth while to screen large numbers of pregnant women for GDM?

Yes : Helps in identifying pregnancies with higher risk for complications like PIH, Hydramnios, Macrosomia (Big Babies), and IUFD (still birth in the womb).

Identify the indications for OGTT.
Use uniform 75G glucose load for OGTT
Diagnostic criteria for GDM to be made uniform by consensus on a region wise basis.
Management of diabetes during pregnancy divided into two broad groups:

Those requiring Insulin

Group I
IDDM or type 1
NIDDM or type 2 controlled on OHA ± insulin and a small percentage of type 2 diabetes mellitus controlled with diet / exercise and IGT and about **10% of Group II cases.**

Those who do not require insulin

All cases of Group III and Group IV (GDM & BLGDM) and majority (90%) of Group II cases.

*To use only Human Insulin during Pregnancy.*

**Control Criteria for Diabetes Pregnancy** There is a good case for using Pyridoxine (Vit.B6) in GDM (Group II to IV) to improve the carbohydrate tolerance; further planned studies would be beneficial. The target blood glucose values, HbA1c, Serum Fructosamire, frequency of blood testing, need for home blood glucose monitoring in IDDM and other exceptionally difficult and high risk pregnancies, all these could be rationalized based on scientific evidence, clinical experience and pragmatic strategies, applicable in day-to-day practice for obtaining maximum qualitative and quantitative benefit could be.
Targets for control of Diabetes in Pregnancy:

1. Fasting: < 110 mg /dl (6.1 mmol /L)
2. Post-Prandial: 140 mg / dl (7.7 mmol / L).
3. HbA1C: 6.5 - 7.5%.
4. Serum Fructosamine: < 3.0 mmol / L.

Maternal and foetal complications associated with diabetes and pregnancy
Higher incidence of PIH (2.2%) and Hydramnios (3.2%), Macrosomia, Peri/Neo Natal morbidity in the new born not different to well managed

Diabetes with Pregnancies & GDM - Though Group I IDDM cases will pose difficult problems.

Congenital anomalies in children - higher in Group I (IDDM and IRDM cases) but not in Group II to IV GDM cases, as compared with non-diabetic pregnancies.
Slightly higher LSCS rate in diabetes pregnancy mainly due to obstetric (maternal / foetal) indications and not due to diabetes. The risk of IUFD especially in IDDM pregnancy and previous BOH has to be constantly borne in mind and monitored very closely during term.

Nutrition in pregnancy needs special counseling and regular monitoring.

Intensive neonatal care is mandatory for infants of diabetic mothers (IDM) in Group I – particularly in IDDM and some IRDM cases.

The confusion over diagnosis, management and understanding of diabetes, pregnancy, and birth should be removed by a planned attempt with

a) National
b) Regional and
c) International working groups and consensus process, which should have defined aims, objectives and goals and an implementation programme within a preset time frame (three to five years).

TEN STEPS TO SUCCESSFUL OUTCOME IN GESTATION DIABETES – www.diabetopaedia.com
Part III

Narrative – Based Medicine
(Illustrative Real time Clinical experience)
Example – 1  Case of Classical Linear Diabetology that is practiced is the so called Sliding Scale Rule in the wards of Hospital, ICU, Post Surgical, Acute Care, Infections etc.

<table>
<thead>
<tr>
<th>Blood Sugar</th>
<th>Insulin Dose (Regular)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;200mg</td>
<td>No Insulin</td>
</tr>
<tr>
<td>201-230</td>
<td>4 units</td>
</tr>
<tr>
<td>231-250</td>
<td>6 units</td>
</tr>
<tr>
<td>251-280</td>
<td>8 units</td>
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<tr>
<td>281-300</td>
<td>10 units</td>
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<tr>
<td>301-350</td>
<td>15 units</td>
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<tr>
<td>351-400</td>
<td>20 units</td>
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<tr>
<td>&gt; 400</td>
<td>Inform the Doctor, mention regarding IV fluids, Calories, etc....</td>
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<tr>
<td>Day</td>
<td>CBG</td>
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<td>Insulin</td>
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<td>Insulin</td>
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*The Importance of checking Insulin delivery & the role of Diabetes Specialist Nurse.*
The Story of Insulin *(In Current Medicine J.R.C.P(E)1988)*

“Insulin is injected subcutaneously, not because this is an appropriate route, but because it is convenient ..... There is considerable day-to-day variation in the speed of absorption from any one site for shoot acting insulin and much greater variation for intermediate acting insulins. It has been calculated that up to 80% of day-to-day variation in blood glucose profiles can be explained by variation in the rate of absorption of intermediate-acting insulin.
The Story of Insulin

“Insulin Delivery to the right place at the right time” R. Taylor in Current Medicine, 1988 Journal of The Royal College of Physicians, Edinburgh.
During the past decade this mega clinical trial with multimega hype was presented to the medical fraternity, VIZ, the results of an exhaustively planned, meticulously implemented, superbly controlled and randomized clinical trial involving 23 centres and 1441 patients with IDDM, and costing over 120 million US$. The findings confirmed (what no sane-thinking diabetologist ever doubted) that “normalizing” blood sugars and HBA1C, throughout the trial period could reduce the micro vascular complications up to 50% or more and even reverse it to a lesser extent. But what was the price to pay?

a. Less than 10% of the participants achieved the target control!

b. 300% more incidence of severe, crippling hypoglycaemia(7) and

c. The protocol used in achieving the near normalization’ of blood sugars and HBA1C in the DCCT trial was so impractical that, even 7 years after the acceptance of the findings of the study by diabetologists the world over, to say that Not even one Centre anywhere in the World implements this type of control in their IDDM patients is indeed the saddest commentary of the usefulness of this mega exercise. Nobody has discussed the why of this aspect in the follow-up. The report is evidently for the archives.
Case Histories

1. The case of Captain S 73 Yrs, (VHS) – Bilateral AKA.
2. Adverse Drug Reactions
   1. Mr. S. 76 Yrs – CAD+ T2DM, Metformin, Acute Fluid Overload with Pulmonary Oedema & Metabolic Acidosis needing Emergency Ventilatory Support.
   2. Mr. M 64 Yrs – T2DM, CAD – Gross Fluid Overload, Anaemia, IHD, CCF & Renal Decompensation (Rosi + Met).
   4. Mrs. I.S 73 Yrs – T2DM + HTN + CAD on Rosi + Met presented with severe (Splitting) bitemporal headache – MRI evidence of bilateral subdural haematoma – increasing drowsiness and deep stupor admitted under Neurologist, seen by Neuro Surgeon planned Burr – Hole Decompression prevented by the Physician because investigations revealed liver dysfunction – Cirrhotic Liver with increased APTT & with conservative treatment she recovered fully & is now doing fine 4 months later.
The relevance of Drugs vs Non Drug Therapy

DM + HTN + Obesity – Mr. R 45 Yrs. Was treated with drugs for 2 years for DM & HTN on 18/12/2004 FBS – 243, PPBS – 494 & BP was 162/102.


Patient was lost for follow – up for 1 year.

24/05/2007 – Routine review when he came to show his mother. No drug therapy for 1 year. Weight 121 Kgs. BP 110/80, Pulse – 76 / Min. Asymptomatic & keeping well.

Treatment – Had stopped Alcohol, Tobacco (Pan Parag) for the past 3 ½ Months.
Is Ayurveda Relevant? – Needs More Authentication

- Case of S.T. 70 Yrs. – T2DM (from 1991) + HTN (from 1980).

1991 – Weight 90 Kgs. BP 150/110. Treatment with Glibenclamide & Atenelol then various drugs.

In 2007 – He complained of the OA of the Knees & was referred to Ayurvedic Physician, who also gave medicines for DM & HTN & at present does not require medication for DM & HTN (PPBS – 138 Mg/dl, HBA1c – 5.4%, BP 130/80, Weight 84.5 Kgs)
Part IV

Conclusions
**Conclusion**

Diabetes is a heredo-familial disorder with a complex genetic inheritance that can manifest in an individual at any age from birth till death and as such it is important to realize that strategies for control of diabetes, particularly drug therapies should pass the test of acceptance without major / significant drug induced *(iatrogenic)* side effects on organs like the Liver, Kidney, Nerves, Eyes etc.

The main aim of drug treatment in diabetes is to achieve sustained control of blood sugars & HBA1C without causing significant or life threatening hypoglycemia.

*Continued...*
Conclusion

Life style modification like diet, exercise, cessation of smoking & Alchohol habit, alteration of stress factors both at home and at work place, individual psycho–social & behavioral factors, all these play important roles in the fluctuations of Glycaemia of the individual patient.

Hence the most important aspect of managing a life long condition like Diabetes Mellitus can be successful only if a proper chronological clear medical record of all events relating to Diabetes & its Co–morbid Conditions, is kept for every case. The value of such a record, during emergencies & routine visits to the Hospital / Doctor, is immeasurable and prevents avoidable medical errors.
Conclusion

- The presently popular paradigm of Absolute Blood Sugar, (HBA1c) control as the Absolute Answer for Avoiding (read postponement or prevention) of major Diabetic complications Absolutely Lakhs evidence.

- Diabetes is perhaps an in-born error in the metabolism of individuals whose genotypes and phenotypes differ as much as their DNAS & RNAS.

All are not created equal.
There is no doubt that the key to successfully keeping Diabetes at bay (read control) lies in;
Maintaining a continuous chronological case record.

Where there are infrastructural facility – EPMRC with follow-up record and co-morbid events with therapy all recorded meticulously with warnings on ADR, Allergies, etc....
Diabetes management has to be customized, always remain holistic (as other co-morbid conditions and their treatment affect DM with Vice versa) and should not be dictated and restricted by guide lines of National or International regulatory/recommendatory bodies (ADA, BDA, EASD, DAI, RSSDI, etc.)

Lastly, the Government and people should discourage unscientific and untenable predictions and Bombardments by direct and indirect promotional efforts through media on Diabetes Epidemiology, Awareness Education, Technology and their imports, Drug Research and their Pros & Cons, etc. In fact there should be an Autonomous consensus Body (National & International) which would sift the wheat from the chaff – promises and performance audit – and inform the public periodically (Is this too much to ask?)

I invite you to visit www.pubmedinfo.com for current medical information on a variety of health related topics.
Finally 32 years ago Oakley, Pyke & Taylor in their book – Diabetes & Its Management (Blackwell Scientific Publications, 1973)

“In general the outlook in diabetes is good although, as in most other diseases, uncertain. The widespread interest in the important ‘complications’ has perhaps exaggerated their severity. We have many patients who have been diabetic for 40 years who are clinically normal, and in those patients who have signs of complications, e.g. a few retinal microaneurysms, there may be no functional defect and no further deterioration. It is sensible, as well as humane, to take a generally optimistic view. Most diabetics lead a full and healthy life, only a minority developing complications which matter (as distinct from those which interest doctors). When complications do appear progress is often unpredictable and treatment is sometimes successful – and methods of treatment are continually improving”.

Continued...
I have sought................for long years I have laboured; but I have not found her ......where I lie down worn out the other men will stand, young and fresh. by steps that I have cut they will climb; but the stairs that I have built they will mount.....At the clumsy work they will laugh ..........they will cruse me. BUT THEY MOUNT AND ON MY WORK;THEY WILL CLIMB AND BY MY STAIR! THEY WILL FIND HER, AND THROUGH ME............

I believe that is all we can really expect from the scientific quest, but that does not make it any less exciting-IT IS THE EXCITING OF THIS ONGOING QUEST THAT SUSTAINS US.
INTEGRATED MEDICINE
ORTHODOX MEETS ALTERNATIVE
Thank You

cvk@diabetopaedia.com