Whither Evidence – Based Medicine?
– The Diabetologist’s Dilemma.

by

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- Head of the V.H.S Diabetes Department – Voluntary Health Services, Chennai.
- Formerly Honorary Clinical Professor & Hony. Physician – Govt. Stanley Medical College & Hospital, Chennai.
- Founder Chairman & Director – HEALTHTRACK INFO SOLUTIONS PVT. LTD.
Friend, Philosopher & Guide to me and many Diabetologists of my Generation & next…

Dr. S.S. Ajgaonkar
Art of Public Speaking

ART OF PUBLIC SPEAKING

BY: Prof. B.M. HEGDE
Preface by: Nani A. Palkhiwala

Bharatiya Vidya Bhavan

Prof. B.M. Hegde
Forty years of Clinical Diabetology Practice, Teaching, Academic
And Research Work, International Committees, Cross Cultural
Perspectives, Fellowship of NAMS,

1. Should you retire & go into oblivion (gardening etc)?

2. Should you pursue a new venture?

3. Should you go–on like a hackney horse till you drop down
dead?
2000-New Millennium – Time to reflect on 35 years of "Progress" in the management of Diabetes

Diabetes in the New Millennium – Quo Vadis Domini
Dr.C.V.Krishnaswami – FRCP(E)., F.A.M.S., D.T.M & H(EDIN)

Do not Follow where the path may lead
Go instead where there is no path and leave a trail.

Ralph Waldo Emerson
“America needs to have sound nutrition education provided to her citizens – of all ages and in all walks of life. We are a nation of nutritionally naive consumers, currently wasting Billions of dollars each year on diet fads and nutrition nonsense”


**Evolution of Diet through the past 100 years**

<table>
<thead>
<tr>
<th>(Pre Insulin) Naunyn Era</th>
<th>No CHO Low fat</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Post Insulin)</td>
<td>Low CHO High Protein, Low fat</td>
</tr>
<tr>
<td></td>
<td>High CHO, Protein, Low fat (Prof. J.C. Patel)</td>
</tr>
<tr>
<td></td>
<td>Relatively high CHO, high Fibre, Adequate protein Low sat fat (Prof. M.V.)</td>
</tr>
</tbody>
</table>

and so on…

Guy’s Hospital Line Protein Diet (Red line, Black line, Green line etc.) Calorie Exchange Diet

Glycaemic Index guided Exchange Diet etc.
William Cullen – 17th Century Edinburgh Physician

“Regularity, flexibility and Moderation”
**The Story of Diet – Sample Diabetic Diet Menu**

**EARLY MORNING 6.30 A.M**
MILK - 150 ml

**BREAKFAST 8.30 A.M**
Idli - 3
Mint Chutney - 2 tbsp
Sambar.

**MID MORNING 10.30 A.M**
Veg Soup - 1 Cup.

**LUNCH 12.30 P.M**
Rice - 2 Cups (100g raw wt)
Drumstick Sambar - ½ Cup
Cabbage Kottu - ¼ Cup
Beans Curry - (100gms)
Curd - 1/2 Cup.

**TEA TIME 3.30 P.M**
Coffee (Milk) - 100 ml
Sprouted Green Gram
Dhal Sundal - ¼ Cup (25 grams)

**MID EVENING 5.30 P.M**
Apple - 1 (Small)

**DINNER 8.00 P.M**
Phulkas - 3
Capsicum Gravy - ½ Cup
Salad

**BED TIME**
MILK - 150 ml
The Story of Diet – Sample Renal Diet Menu

**EARLY MORNING 6.30 A.M**
MILK - 100ml

**BREAK FAST 8.30 A.M**
IDIYAPPAM-3
TOMATO CHUTNEY-2tbsp

**MID MORNING 10.30 A.M**
THIN BUTTER MILK - 150ml

**LUNCH 12.30 P.M**
MIXED VEGETABLES RICE-2CLIPS
(Carrot, Beans, Cauliflower, Onion)
(leached)
Ladies Finger Raita(Curd 50 ml)

**TEA TIME 3.30 P.M**
MILK - 100ml
MARIE BISCUIT-3

**MID EVENING 5.30 P.M**
GUAVA-1 (Medium Size-low in K+)

**DINNER 8.00 P.M**
PHULKAS -3
PANNER CAPSICUM GRAVY-1 CLIP

**BED TIME**
MILK-100ml
The Story of Physical Exercise (including yoga)

Asanas For General Use

- **PADMASAN**
  - Lotus
- **PADA-UTTAN**
  - Leg-Lift
- **BHUJANGASAN**
  - Cobra
- **SALABHASAN**
  - Locust
- **MATSYASAN**
  - Fish
- **DHANURASAN**
  - Bow
- **SHAVASAN**
  - Relaxation
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.
“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 insulins and much greater variation for intermediate acting insulins. It has been calculated that upto 80% of day-to-day variation in blood glucose profiles can be explained by variation in the rate of absorption of intermediate-acting insulins.
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 microvascular complications upto 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.
# 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>
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 stroke 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)\(^5\).
Shame: the elephant in the room
Managing shame is important for improving health care


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?
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 chlorpropamide developed high B.R and hence it was withdrawn from the study.

b. In a randomized substudy, 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 upword 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!!.
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 these 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 NH₄⁺ formation which is quite often implicated in sodium exchange (Rooth and Bandman, 1973).


JOUR. DIAB. ASSO. IND. : VOL XIX. IAN, 1979
B. 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.
In the United Kingdom it has been shown that doctors tend not to comply both these contraindications. **In Southampton 54% of 89 patients treated with metformin had a published contraindication. “In Dundee recent analysis of 1847 patients treated with Metformin showed that a 24.5% (452) had a contraindication to Metformin.**

A simplified and pragmatic set of guidelines should be adapted, **stressing the importance of renal clearance of Metformin and withdrawal of Metformin in patients with tissue hypoxia.** We hope that this suggested guidelines are less ambiguous than current ones and prevent the current situation of many clinicians, who r having to ignore return contraindications in order to maximize the use of metformin appropriately.
What is Evidence?

M.J.Campbell in “Chronic Wound Management

Evidence Based, Healthcare (EBHC) requires that we should **consider critically all evidence that a treatment works or an agent causes a disease.**

Sackett and co-workers give an example of finding that patients who displayed ventricular ectopic beats following a myocardial infarction were at high risk of sudden death. Drugs then were widely prescribed to suppress these ectopics, on the assumption that removing the cause would reduce the effect. However subsequent randomized controlled trails, which examined clinical outcomes and not physiologic process, showed that use of these drugs actually **increased death rates** rather than decreased them **and their use is now strongly discouraged.**
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 Health Carers 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).
“Rosiglitazone – Useful Drug but has Side Effects”

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.

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

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
## Prevalence of Type – 2 Diabetes Mellitus in India

<table>
<thead>
<tr>
<th>Year</th>
<th>Population of India (in millions)</th>
<th>Prevalence (in millions)</th>
<th>Percentage (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2002</td>
<td>1000 +</td>
<td>30</td>
<td>3.0</td>
</tr>
<tr>
<td>2025</td>
<td>1250 +</td>
<td>57</td>
<td>4.5</td>
</tr>
</tbody>
</table>

*(WHO Projections – 1999)*
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.

<table>
<thead>
<tr>
<th>Year</th>
<th>Author</th>
<th>Place</th>
<th>Area</th>
<th>Urban</th>
<th>Rural</th>
</tr>
</thead>
<tbody>
<tr>
<td>1971</td>
<td>Tripathy et al</td>
<td>Cuttack</td>
<td>(Central)</td>
<td>1.2</td>
<td></td>
</tr>
<tr>
<td>1972</td>
<td>Ahuja et al</td>
<td>New Delhi</td>
<td>(North)</td>
<td>2.3</td>
<td></td>
</tr>
<tr>
<td>1979</td>
<td>Gupta et al</td>
<td>Multicentre</td>
<td></td>
<td></td>
<td>3.0</td>
</tr>
<tr>
<td>1984</td>
<td>Murthy et al</td>
<td>Tenali</td>
<td>(South)</td>
<td>4.7</td>
<td>1.3</td>
</tr>
<tr>
<td>1986</td>
<td>Patel</td>
<td>Bhadran</td>
<td>(West)</td>
<td>3.8</td>
<td></td>
</tr>
<tr>
<td>1988</td>
<td>Ramachandran et al</td>
<td>Kudremukh</td>
<td>(South)</td>
<td>5.0</td>
<td></td>
</tr>
<tr>
<td>1989</td>
<td>Kodali et al</td>
<td>Gangavathi</td>
<td>(South)</td>
<td>2.2</td>
<td></td>
</tr>
<tr>
<td>1989</td>
<td>Rao et al</td>
<td>Eluru</td>
<td>(South)</td>
<td>1.6</td>
<td></td>
</tr>
<tr>
<td>1991</td>
<td>Ahuja et al</td>
<td>New Delhi</td>
<td>(North)</td>
<td>6.7</td>
<td></td>
</tr>
<tr>
<td>1992</td>
<td>Ramachandran et al</td>
<td>Madras</td>
<td>(South)</td>
<td>8.2</td>
<td>2.4</td>
</tr>
<tr>
<td>1997</td>
<td>Ramachandran et al</td>
<td>Madras</td>
<td>(South)</td>
<td>11.6</td>
<td></td>
</tr>
<tr>
<td>2000</td>
<td>Ramankutty et al</td>
<td>Kerala</td>
<td>(South)</td>
<td>12.4</td>
<td>2.5</td>
</tr>
<tr>
<td>2001</td>
<td>Ramachandran et al</td>
<td>National Urban (DESI)</td>
<td></td>
<td>12.1</td>
<td></td>
</tr>
<tr>
<td>2001</td>
<td>Misra et al</td>
<td>New Delhi</td>
<td>(North)</td>
<td>10.3</td>
<td></td>
</tr>
<tr>
<td>2002</td>
<td>Mohan et al</td>
<td>Chennai</td>
<td>(South)</td>
<td>12.1</td>
<td></td>
</tr>
<tr>
<td>2004*</td>
<td>Shaukat et al</td>
<td>National</td>
<td></td>
<td>5.6</td>
<td>2.7</td>
</tr>
</tbody>
</table>

* Different sample selection criteria
The I.I.T Study - 1992 – 1993 (Conducted by The VHS Diabetes Department, Chennai.

<table>
<thead>
<tr>
<th>Sex (N)</th>
<th>Normal (%)</th>
<th>IGT (%)</th>
<th>DM(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male (N 663)</td>
<td>450 (67.9%)</td>
<td>155 (23.4%)</td>
<td>58 (8.7%)</td>
</tr>
<tr>
<td>Female (N 419)</td>
<td>275 (65.6%)</td>
<td>120 (28.6%)</td>
<td>24 (5.7%)</td>
</tr>
<tr>
<td>Total (1082)</td>
<td>725 (66%)</td>
<td>275 (26%)</td>
<td>82 (8%)</td>
</tr>
</tbody>
</table>
Prevalence and Incidence of Type - 2 Diabetes and Impaired Glucose Tolerance in a Selected Indian Urban Population

The I.I.T Study - 1992 – 1993 (Conducted by The VHS Diabetes Department, Chennai.

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%
Prevalence of Known Diabetes in Chennai – Jointly by The VHS Diabetes Department & The National Institute of Epidemiology, Chennai.

<table>
<thead>
<tr>
<th>AGE (YRS)</th>
<th>MALES</th>
<th>FEMALES</th>
<th>TOTAL</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PEOPLE</td>
<td>DIABETES</td>
<td>PREVELANCE</td>
</tr>
<tr>
<td>0-9</td>
<td>2066</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>10-14</td>
<td>1267</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>15-19</td>
<td>1374</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>20-24</td>
<td>1353</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>25-29</td>
<td>1350</td>
<td>5</td>
<td>0.4</td>
</tr>
<tr>
<td>30-34</td>
<td>1168</td>
<td>7</td>
<td>0.6</td>
</tr>
<tr>
<td>35-39</td>
<td>1094</td>
<td>23</td>
<td>2.1</td>
</tr>
<tr>
<td>40-44</td>
<td>908</td>
<td>42</td>
<td>4.6</td>
</tr>
<tr>
<td>45-49</td>
<td>818</td>
<td>56</td>
<td>6.8</td>
</tr>
<tr>
<td>50-54</td>
<td>604</td>
<td>72</td>
<td>11.9</td>
</tr>
<tr>
<td>55-59</td>
<td>425</td>
<td>61</td>
<td>14.4</td>
</tr>
<tr>
<td>60-64</td>
<td>389</td>
<td>46</td>
<td>11.8</td>
</tr>
<tr>
<td>65-69</td>
<td>223</td>
<td>34</td>
<td>15.2</td>
</tr>
<tr>
<td>70+</td>
<td>327</td>
<td>38</td>
<td>11.6</td>
</tr>
<tr>
<td>TOTAL</td>
<td>13366</td>
<td>384</td>
<td>2.9</td>
</tr>
</tbody>
</table>
The scandal of poor medical research
We need less research, and research done for the right reasons

- 284  BMJ volume 308 29 January 1994

What, then, should we think about researchers who use the wrong techniques (either willfully or in ignorance), use the right techniques wrongly, misinterpret their results, report their results selectively, cite the literature selectively, and draw unjustified conclusions? We should be appalled. Yet numerous studies of the medical literature, in both general and specialist journals have shown that all of the above phenomena are common. This is surely a scandal.

Douglas G. Altman – Head Medical Statistical Laboratory Imperial Cancer Research Fund, LONDON.

Do epidemiologists cause epidemics?

THE LANCET – VOL 341: APRIL 17, 1993

“Epidemiology – is it time to call it a day?”

- International Journal of Epidemiology
Editorial

Reply by

Dr. C.V. Krishnaswami – Head of the Diabetes Department, Voluntary Health Service Hospital, Chennai
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.
Life style modification like diet, exercise, cessation of smoking habit, moderating intake of alcohol, 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.

DIABETOPAEDIA.COM – Meeting the challenges of Providing Information for Doctors, Patients and Health-Carers in Diabetes.

The above two papers were presented during the conference organised by the 7 Royal Colleges of Physician & Surgeon of Scotland and The British Medical Journal publishing group in October-2002
Benefits of using Online Electronic Medical Record

- I am able to contact my doctor from anywhere!
- I am able to store & view my records anytime anywhere!!
- I don't carry bulky files when I meet my doctor!!!

How about U???

21st Century Medical Care at your fingertips...
Thank You

cvk@diabetopaedia.com