Reviewing Ethical Issues in Endocrinology Research

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• The subjects of endocrinology are very vast
• It extends from widely prevalent disease of diabetes mellitus to assisted reproduction technique i.e. common disease to modern technology oriented problem
# World Burden of Diabetes

## AT A GLANCE

<table>
<thead>
<tr>
<th></th>
<th>2007</th>
<th>2025</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total world population (billions)</td>
<td>6.6</td>
<td>7.9</td>
</tr>
<tr>
<td>Adult population (age 20-79, billions)</td>
<td>4.1</td>
<td>5.2</td>
</tr>
</tbody>
</table>

## WORLD DIABETES AND IGT (20-79 age group)

### Diabetes

<table>
<thead>
<tr>
<th></th>
<th>2007</th>
<th>2025</th>
</tr>
</thead>
<tbody>
<tr>
<td>Comparative prevalence (%)</td>
<td>6.0</td>
<td>7.3</td>
</tr>
<tr>
<td>Number of people with diabetes (millions)</td>
<td>246</td>
<td>380</td>
</tr>
</tbody>
</table>

### IGT

<table>
<thead>
<tr>
<th></th>
<th>2007</th>
<th>2025</th>
</tr>
</thead>
<tbody>
<tr>
<td>Comparative prevalence (%)</td>
<td>7.5</td>
<td>8.0</td>
</tr>
<tr>
<td>Number of people with IGT (millions)</td>
<td>308</td>
<td>418</td>
</tr>
</tbody>
</table>

Global Projections for the Diabetes Epidemic: 2000-2030 (in millions)

- NA
  - 2000: 19.7
  - 2030: 33.9
  - Increase: 72%

- LAC
  - 2000: 13.3
  - 2030: 33.0
  - Increase: 248%

- EU
  - 2000: 17.8
  - 2030: 25.1
  - Increase: 41%

- SSA
  - 2000: 7.1
  - 2030: 18.6
  - Increase: 261%

- MEC
  - 2000: 20.1
  - 2030: 52.8
  - Increase: 263%

- China
  - 2000: 20.8
  - 2030: 42.3
  - Increase: 204%

- A+NZ
  - 2000: 1.2
  - 2030: 2.0
  - Increase: 65%

World
- 2000 = 171 million
- 2030 = 366 million
- Increase 213%

Diabetes Care 2004 In press
### Prevalence studies in India

<table>
<thead>
<tr>
<th>Year</th>
<th>Author</th>
<th>Place</th>
<th>Prevalence (%)</th>
<th>Remark</th>
</tr>
</thead>
<tbody>
<tr>
<td>1972</td>
<td>Ahuja et al</td>
<td>ICMR multicentric study</td>
<td>2.1</td>
<td>Multicentric</td>
</tr>
<tr>
<td>1988</td>
<td>Ramchandran et al</td>
<td>Kudremukh</td>
<td>5.0</td>
<td>Survey of township</td>
</tr>
<tr>
<td>2000</td>
<td>Raman Kutty et al</td>
<td>Thiruvananthapuram</td>
<td>12.4</td>
<td>Urban settlement</td>
</tr>
<tr>
<td>2001</td>
<td>Mohan et al</td>
<td>Chennai</td>
<td>12.0</td>
<td>Survey of two income groups</td>
</tr>
<tr>
<td>2001</td>
<td>Ramchandran et al</td>
<td>NUDS (six centre)</td>
<td>12.1</td>
<td>Multicentric</td>
</tr>
<tr>
<td>2002</td>
<td>Gupta et al</td>
<td>Jaipur</td>
<td>12.7</td>
<td>Only FBS</td>
</tr>
<tr>
<td>2005</td>
<td>Raman et. Al</td>
<td>Lucknow</td>
<td>18%</td>
<td>FBS &amp; PGBS</td>
</tr>
</tbody>
</table>
Ethics in Diabetic Clinical Trials
Ethics in Diabetic Clinical Trials

• Many of the placebo-controlled trials currently being performed to assess new oral diabetic therapies do not meet ethical standard.

• Comparing an experimental drug with a placebo is perfectly ethical when no proven effective therapy exists and when the risk-to-benefit ratio needs to be assessed.
Ethics in Diabetic Clinical Trials

- However, when effective therapy exists, the use of placebo control subjects does not meet the ethical standard.

- In these situations, the efficacy and safety of the experimental medication should be tested by blindly randomizing one group to the experimental drug and the other group to an existing drug that has been shown as effective and safe.
Ethics in Diabetic Clinical Trials

• As investigators, how long can we ethically permit hyperglycemia to continue in diabetic subjects randomized to placebo therapy?

• Indeed, 6 months of hyperglycemia will have an adverse effect on the quality of life, and could possibly be long enough for microvascular complications that would not have occurred with better glycemic control to occur.

• We should not encourage the use of placebo controlled trials when a proven effective and safe alternative therapy is available.
Ethical Issues of Predictive Genetic Testing for Diabetes
Ethical Issues of Predictive Genetic Testing for Diabetes

• Type 2 diabetes mellitus (T2DM) is a prevalent, chronic condition associated with extensive morbidity, decreased quality of life, and increased utilization of health services.

• The polygenic nature of T2DM has been a major challenge to identifying genes involved in the pathogenesis of this disease knowledge that could give rise to new treatments and tests.

• Many professional groups strongly discourage genetic testing for children unless immediate clinical benefit can be gained.
Ethical Issues of Predictive Genetic Testing for Diabetes

- So, predictive testing for T2DM would likely be discouraged and testing delayed until adulthood
- Potential harms include the risk of stigmatization, discrimination, and other adverse psychosocial impacts
Type 1 DM: Ethical Issues in Research with Children
Type 1 DM: Ethical Issues in Research with Children

• As a result, HLA genotyping can be used to identify children at increased risk for type 1 diabetes mellitus; research studies to evaluate this testing strategy are currently being implemented.

• Research involving children raises significant questions, and families may need guidance in considering the risks and benefits of participation.
Type 1 DM: Ethical Issues in Research with Children

Important guideline for research involving children

- The degree of risk to the child, the direct benefit to the child, and the direct benefit to other children
- The process for soliciting the assent of children and the permission of parents and guardians
- The nature of the health problem under study. The more serious the problem for children, the greater the claim that research could be justified
Queries by parents

- Medical benefits from participation for child?
- Study participation coordinated with medical care?
- Will research participation provide a clinical benefit to the family?
- Will research participation pose a risk to the family?
Ethical issues in thyroid disease
Introduction

• Hypothyroidism is common disorder, affect women more than men and incidence increases with age

• In community survey in UK (Whickham study)
  – abnormally high serum TSH in men: 2.8%, women: 7.5%

• In NHANES III (survey US)
  – age more than 65 yr, overt hypothyroid:1.7%, mild:13.7%

• Functional studies of the goitrous subjects showed overall prevalence of 1.9% hyperthyroidism

• Thyroid cancer , Incidence 3.6 per lacs to 8.7% per lacs
Informed Consent

• The components of valid informed consent comprise full disclosure of diagnosis, and planned therapies for autonomous patients.

• A signature on a consent form does not necessarily mean that valid informed consent has occurred (Graves’ disease- RIA).

• Patients who do not have decision-making capacity require a surrogate decision maker.
Informed Refusal and Noncompliance in Thyroidology

• The Principle of Respect for Persons obligates physicians to respect the preferences of autonomous patients

• This means that patients may accept or refuse recommended treatments
End-of-Life Decision Making in Thyroidology

- End-of-life decision making generally arises in the context of patients suffering from aggressive thyroid cancer that no longer responds to treatment.
- For such patients, advance care planning should occur, with all of the following options discussed:
  - Prognosis
  - Treatment options
  - Preferences regarding nutrition, hydration, and intubation
  - Palliative care
Genomic Issues in Thyroidology

• There are many psychosocial barriers to genetic screening, which must be recognized.

• The following should be considered in patients undergoing genetic screening:
  – Positive results and psychosocial consequences
  – Potential for false-positive or false-negative results
  – Duty to warn
  – Screening in pediatric populations
  – Obtaining genetic material for research
Ethical challenges in osteoporosis research
Prevalence of Low Femoral Bone Density in Older U.S. Adults from NHANES III

• Recent data from the NIH’s Third National Health and Nutrition survey

• Women
  – Osteoporosis 13-18% (4-6 million)
  – Osteopenia 37-50% (13-17 million)

• Men
  – Osteoporosis 3-6% (1-2 million)  [1-4% (280,000-1 million)]
  – Osteopenia 28-47% (8-13 million)  [15-33% (4-9 million)]
Estimates of Prevalence of Low Bone Mass and Osteoporosis from National Osteoporosis Foundation 2002 figures

Ethical challenges in osteoporosis research

• The approval process for new osteoporosis drugs and the ethics surrounding placebo-controlled, randomized clinical trials used to test investigational drugs is often accompanied by controversy
Ethical challenges in osteoporosis research

• The controversy about clinical trials in osteoporosis is primarily focused on two points:
  – the inclusion of participants who are highly susceptible to fractures, thus at risk from random assignment to placebo, and
  – fracture used as a primary endpoint
**Ethical challenges in osteoporosis research**

- **Two views**
  - Placebo-controlled trials of investigational osteoporosis agents are safe if researchers “proceed with caution.”
  - But
  - “placebo-controlled studies with fracture endpoints in patients with osteoporosis will nearly always be unethical.”
Ethical standard for research - WMA

- Clinical studies intended to support new drug applications, also called registration or pivotal trials.
- Placebo-controlled groups allow a clear assessment of the safety and efficacy of an active drug while limiting confounding factors.
- The difficulty arises in studies of serious or potentially life-threatening conditions for which effective treatments exist.
- “The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best current proven intervention.”

The World Medical Association’s Declaration of Helsinki
Ethics of withholding treatment

A good example of a recent, large, placebo-controlled, randomized clinical trial in the field of osteoporosis research is the FREEDOM study, which evaluated the safety of denosumab (Prolia, Amgen) and found beneficial effects on vertebral and nonvertebral fracture protection.

“Osteoporotic hip and vertebral fractures have serious consequences, including increased risk of death, surgical procedures and long-term impairment of physical function.”
Another issue is the inclusion of patients with severe disease — and the greatest risk for fracture. “This debate is often framed by the simple question of whether people who are highly susceptible to an osteoporotic fracture should be involved in a clinical trial.” “With use of appropriate guidelines to exclude high-risk patients”
Fracture as a primary endpoint

“An agent preserves or enhances bone mass provides only suggestive evidence that it reduces fracture risk; fracture studies must be done to document reduction of fracture incidence”

- It believes that these concerns “can be cured by performing active comparator research with rescue therapy provisions included”
- Although such a design may increase the costs and size of trials for osteoporosis
Embryonic stem cells - Ethical issue

- Stem cell research could provide a means of replacing damaged tissue in patients with diabetes
- Embryos are a potentially rich source of viable stem cells
- Cloned embryos may one day allow the customised replacement of damaged tissues and organs
- The morality of undertaking such research is hotly contested
A philosophically coherent approach to embryo research would acknowledge the intrinsic value accorded by people to all human life. Society must find a way to reconcile these intuitive concerns with the utilitarian desire to maximise the benefits of stem cell research.
Assisted reproductive technology (ART)

- Assisted reproductive technology (ART) is currently a common place technology
- Explosion of this technology has introduced a myriad of new social, ethical, and legal challenges
- The ethical issues which arise are the autonomy and long-term welfare of individuals (both men and women) who take part in ART or research; the need for informed decision making; the importance of an ethical framework for the use of gametes and embryos in clinical practice, training and research
Assisted reproductive technology (ART)

- It would also acknowledge the desire to realize the benefits that new technology offers
Ethical guidelines for research - Summary

- Respect all participants
- Respect human embryos
- Do not use any unacceptable or prohibited practices
- Minimise risks
- Offer separate decision-making processes
- Provide information
- Obtain consent
- Keep detailed records
- Assess and monitor outcomes for all participants
Ethical guidelines for research- Summary

- Disclose financial interests
- Respect conscientious objections
Thank You