Defining Key Challenges in Diabetes Mellitus

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Agenda

- Diabetes mellitus as a global disease.
- Diabetic retinopathy and its risk factors
- Relation between DME and cardiovascular complications
- Anti VEGF role in treatment of DME
New estimates for 2012 of diabetes prevalence, mortality, and healthcare expenditures
More than 371 million people have diabetes.

TOP 10 COUNTRIES/TERRITORIES FOR PEOPLE WITH DIABETES (20-79 YEARS)

- China: 92.3 million
- India: 63.0 million
- USA: 24.1 million
- Brazil: 13.6 million
- Russia: 12.7 million
- Mexico: 10.6 million
- Indonesia: 7.6 million
- Egypt: 7.5 million
- Japan: 7.1 million
- Pakistan: 6.6 million

The number of people with diabetes is increasing in every country.

TOP 10 COUNTRIES/TERRITORIES FOR PREVALENCE* (%) OF DIABETES (20-79 YEARS)

<table>
<thead>
<tr>
<th>COUNTRY / TERRITORY</th>
<th>PREVALENCE (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1  Federated States of Micronesia</td>
<td>37.2</td>
</tr>
<tr>
<td>2  Nauru</td>
<td>30.1</td>
</tr>
<tr>
<td>3  Marshall Islands</td>
<td>27.1</td>
</tr>
<tr>
<td>4  Kiribati</td>
<td>25.5</td>
</tr>
<tr>
<td>5  Tuvalu</td>
<td>24.8</td>
</tr>
<tr>
<td>6  Kuwait</td>
<td>23.9</td>
</tr>
<tr>
<td>7  Saudi Arabia</td>
<td>23.4</td>
</tr>
<tr>
<td>8  Qatar</td>
<td>23.3</td>
</tr>
<tr>
<td>9  Bahrain</td>
<td>22.4</td>
</tr>
<tr>
<td>10 Vanuatu</td>
<td>22.0</td>
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</tbody>
</table>

*comparative prevalence
### Top 10: Countries/territories of number of people with diabetes (20-79 years), 2011 and 2030

<table>
<thead>
<tr>
<th>Country/Territory</th>
<th>2011 Millions</th>
<th>2030 Millions</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. China</td>
<td>90.0</td>
<td>129.7</td>
</tr>
<tr>
<td>2. India</td>
<td>61.3</td>
<td>101.2</td>
</tr>
<tr>
<td>3. United States of America</td>
<td>23.7</td>
<td>29.6</td>
</tr>
<tr>
<td>4. Russian Federation</td>
<td>12.6</td>
<td>19.6</td>
</tr>
<tr>
<td>5. Brazil</td>
<td>12.4</td>
<td>16.8</td>
</tr>
<tr>
<td>6. Japan</td>
<td>10.7</td>
<td>16.4</td>
</tr>
<tr>
<td>7. Mexico</td>
<td>10.3</td>
<td>14.1</td>
</tr>
<tr>
<td>8. Bangladesh</td>
<td>8.4</td>
<td>12.4</td>
</tr>
<tr>
<td>9. Egypt</td>
<td>7.3</td>
<td>11.8</td>
</tr>
<tr>
<td>10. Indonesia</td>
<td>7.3</td>
<td>11.4</td>
</tr>
</tbody>
</table>

### Half of people with diabetes don’t know they have it.

**Undiagnosed percentage and undiagnosed cases of diabetes (20-79 years) by region**

- **Africa**: 81% (12 million cases)
- **Europe**: 39% (21 million cases)
- **Middle East and North Africa**: 53% (16 million cases)
- **North America and the Caribbean**: 29% (11 million cases)
- **South and Central America**: 45% (12 million cases)
- **South-East Asia**: 51% (9 million cases)
- **Western Pacific**: 58% (7 million cases)
- **World**: 61% (187 million cases)
Half of people who die from diabetes are under the age of 60.

DEATHS ATTRIBUTABLE TO DIABETES BY AGE (20-79 YEARS)

4.8 million people died and 471 billion USD were spent due to diabetes in 2012.

HEALTHCARE EXPENDITURES AND DEATHS PER 1,000 DUE TO DIABETES BY INCOME GROUP
The burden and costs of chronic diseases in low-income and middle-income countries

The Lancet 5, December 2007
T2DM trends in Egypt - Complications & Risk factors (NIDE Data 2008)

Prevalence (%)

- High Cholesterol
- Low HDL
- Hypertension
- Retinopathy
- Nephropathy
- Neuropathy

Diabetic Retinopathy
Diabetic Retinopathy

- It is a well-characterized, sight-threatening, chronic ocular disorder that eventually develops to some degree in nearly all patients with diabetes.[1]

- After 20 years’ duration, evidence of retinopathy is present in almost all patients with type 1 and up to 80% with type 2 diabetes.[2]

- It is the leading cause of blindness among adults aged 20-74 years; each year it causes 12,000-24,000 new cases of blindness in the United States alone.[3]
The risk factors associated with retinopathy progression include:

1. Duration of diabetes
2. Hyperglycemia
3. Hypertension
4. Hyperlipidemia
5. Pregnancy
6. Renal diseases
7. Anaemia

Duration of Diabetes

- Time is the most important risk factor for the development of DR.
- Retinopathy is uncommon in the initial 3-5 years after diagnosis of type 1 diabetes.
- The risk of developing proliferative disease also increases with time.
- In type 2 diabetes it is often difficult to determine the exact duration of disease, but at the time of diagnosis, up to a fifth of patients may have established retinopathy.
- Earlier studies indicated that of those who were asymptomatic at presentation, approximately 10% will have non-proliferative disease at 10 years, 40% at 15 years, and 60% at 20 years.

Metabolic Control (control of hyperglycemia)

- Epidemiological trials (namely DCCT and UKPDS) established the importance of intensive blood glucose control in reducing the risk of micro vascular complications (target HbA1c level, 7%).


Blood Pressure

- Patients with diabetes and hypertension are more likely to develop more severe levels of DR and have more rapid progression compared with patients with diabetes but without hypertension.

- Diffuse macular oedema is also more common in people with both diabetes and hypertension.

- The UKPDS showed that treating hypertension reduced microvascular and macro vascular complications.

- The ABCD (Appropriate Blood pressure Control in Diabetes) trial found that lowering the diastolic pressure, even in normotensive patients, slowed the progression of DR and nephropathy along with lowering the incidence of stroke.
Elevated Serum Lipid Levels

- Elevated serum lipid levels, especially low-density lipoprotein (LDL) and triglyceride levels, not only contribute to significant cardiovascular morbidity but also increase severity of retinopathy.
- Higher levels of serum cholesterol are associated with increased severity of retinal hard exudates.

Pregnancy

- Pregnancy causes a worsening of DR.
- DR is worsened by pregnancy, but this is essentially a transient progression.
- Pregnancy presumably worsens retinopathy by altering retinal hemodynamic, and increased progesterone may induce intraocular VEGF production.
Renal Disease

- Renal disease is a complication of longstanding diabetes. Its frequent co-occurrence with retinopathy reflects the fact that common predisposing factors underlie both disorders.

- End-stage renal disease may further worsen retinopathy because of its associated haemostatic abnormalities, and its effect on blood pressure regulation.

- The presence and severity of DR are indicators of the risk of renal problems, whereas proteinuria predicts development of PDR.

- Hence, patients with advanced diabetic renal disease need to be monitored closely for worsening of retinopathy and vice versa.

Anaemia

- Anaemia has a deleterious effect on DR.

- Patients with diabetes and low haemoglobin levels have a 5-fold increased risk of severe retinopathy than those with higher haemoglobin levels.

- Increasing Haematocrit has been shown to be beneficial in resolving macular oedema and improving visual acuity in patients with diabetes and anaemia.

References:


Relationship between DR and CVD

Do patients with DR have a higher risk for CVD?
**DR and Cardiovascular diseases**

- The World Health Organization Multinational Study of Vascular Disease in Diabetes (WHO-MSVDD) consists of a large cohort of type 1 and 2 diabetic persons who were followed up for 12 years for incidence of fatal and non-fatal cardiovascular outcomes (Fuller et al., 2001).

- In the WHO-MSVDD, the presence of diabetic retinopathy predicted higher risk of cardiovascular disease and mortality (Fuller et al., 2001).

- Studies have also shown a “dose-dependent” association between increasing severity of diabetic retinopathy and increasing cardiovascular disease risk (Henricsson et al., 1997; Jager et al., 2001; Juutilainen et al., 2007; Klein et al., 2002a; Rajala et al., 2000; Targher et al., 2006; Van Hecke et al., 2003; van Hecke et al., 2005).

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**DR and heart diseases**

- There are clinical studies that suggest the presence of retinopathy can be used as an indicator of silent myocardial ischemia (Araz et al., 2004; Gokcel et al., 2003; Janand-Delenne et al., 1999; Naka et al., 1992; Norgaz et al., 2005; Yoon et al., 2001).
DR and heart diseases

- The population-attributable risk of retinopathy to heart failure has been estimated to be 30.5% in people with diabetes without a previous history of myocardial infarction and hypertension, suggesting that nearly one third of these diabetic cardiomyopathy cases was related to microvascular dysfunction (Wong et al., 2005b).

DR and Cerebrovascular accidents

- More recently, the Atherosclerosis Risk in Communities (ARIC) study, a large prospective cohort study of 1,617 middle-aged white and black Americans with type 2 diabetes, showed that the presence of NPDR, was associated with a two to three-fold higher risk of ischemic stroke. (Cheung et al., 2007c; Wong et al., 2001a).
Do patients with DME have a higher risk for CVD?

Study design and sample

- A retrospective cohort study design was used to compare incidence rates of hospitalized MI and CVA in patients with DME and diabetic patients without retinal disease. Claims were analyzed for the 4-year period from 1 January 2002 to 31 December 2005.

- For an estimated sample of 3,000 subjects with DME, there was over 80% power to detect a hazard ratio of at least 1.25 with 95% confidence (i.e., 25% increased risk of a CV event) within either group.

- Patients were matched by gender and age using the following fixed ranges: 18–25, 26–30, 31–35, 36–40 years, and so on, through to 86+ years. Each control subject was assigned the same index date as the corresponding DME subject.

Nguyen-Khoa et al. BMC Ophthalmology 2012, 12:11
Results

DME and Myocardial infarction

- After adjustment for risk factors and CCI score, the rate of MI events was significantly higher in the DME group than in controls (adjusted HR 2.50, 95% CI: 1.83-3.41, p<0.001). The presence of heart disease, history of MI, and prior use of antiplatelet or anticoagulant drugs were significant positive predictors of MI in the regression model.

Results

DME and cardiovascular accidents

- The rates of CVA were also higher in the DME group for both genders. In particular, the crude risk of stroke in men with DME was 2-times higher than in the control group, and nearly 3-times higher in women with DME.
Recommendations: Retinopathy

- To reduce the risk or slow the progression of retinopathy
  - Optimize glycemic control (A)
  - Optimize blood pressure control (A)

Recommendations: Retinopathy Screening (1)

- Initial dilated and comprehensive eye examination by an ophthalmologist
  - Adults and children aged 10 years or older with type 1 diabetes
    • Within 5 years after diabetes onset (B)
  - Patients with type 2 diabetes
    • Shortly after diagnosis of diabetes (B)

Recommendations: Retinopathy Screening (2)

- Subsequent examinations for type 1 and type 2 diabetic patients (B)
  - Should be repeated annually by an ophthalmologist
- Less frequent exams (every 2–3 years) (B)
  - May be considered following one or more normal eye exams
- More frequent examinations required if retinopathy is progressing (B)

Recommendations: Retinopathy Screening (3)

- High-quality fundus photographs
  - Can detect most clinically significant diabetic retinopathy (E)

- While retinal photography may serve as a screening tool for retinopathy, it is not a substitute for a comprehensive eye exam
  - Perform comprehensive eye exam at least initially and at intervals thereafter as recommended by an eye care professional (E)


Recommendations: Retinopathy Screening (4)

- Women with preexisting diabetes who are planning pregnancy or who have become pregnant (B)
  - Comprehensive eye examination
  - Counseled on risk of development and/or progression of diabetic retinopathy

- Eye examination should occur in the first trimester (B)
  - Close follow-up throughout pregnancy
  - For 1 year postpartum

Recommendations: Retinopathy Treatment (1)

- Laser photocoagulation therapy is indicated (A)
  - To reduce risk of vision loss in patients with
    - High-risk PDR
    - Clinically significant macular edema
    - Some cases of severe NPDR

Recommendations: Retinopathy Treatment (2)

- Anti-vascular endothelial growth factor (VEGF) therapy is indicated for diabetic macular edema (A)

- Presence of retinopathy
  - Not a contraindication to aspirin therapy for cardio protection, as this therapy does not increase the risk of retinal hemorrhage (A)
Discussion

- One implication of quantifying baseline rates of cardiovascular events in DME is the advent of agents that locally suppress vascular endothelial growth factors (VEGF) in the retina but that may also have systemic effects.

- Studies have shown that VEGF inhibitors may be effective in treating DME. However, if VEGF inhibition reaches the systemic circulation, it may play a role in potentiating cardiovascular complications in diabetes.

- As they are adopted into clinical practice, additional population research will be needed to evaluate the long term safety of advanced drugs that target the microvascular complications of diabetes.

What role does VEGF play in cardiac & retinal tissues?

<table>
<thead>
<tr>
<th>Cardiac tissues</th>
<th>Expression of VEGF and VEGF-R</th>
<th>Retinal tissues</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Positive effect</strong></td>
<td>Promote collateral vascular formation in response to ischemia</td>
<td></td>
</tr>
<tr>
<td><strong>Negative effect</strong></td>
<td>• Swelling of the retina • Thickening of the basement membrane • Increased permeability and leakage of plasma constituents in the surrounding retina, resulting in retinal edema</td>
<td></td>
</tr>
</tbody>
</table>
Summary

- DR is a widely prevalent disease and a common cause of visual loss.
- It can progress in the absence of symptoms, producing irreversible damage to the retina.
- The key to managing this ailment is realizing that prevention is better than treatment.
- Interventions are most efficacious when started early in the disease, when retinal damage is minimal and clinical findings are few or absent.
- Regular screening examinations along with intensive control of hyperglycaemia, serum lipid levels, and blood pressure not only retard the progression of DR but also contribute to reducing cardiovascular mortality.
- Studies have shown that VEGF inhibitors may be effective in treating DME. However, if VEGF inhibition reaches the systemic circulation, it may play a role in potentiating cardiovascular complications in diabetes.
- Additional population research will be needed to evaluate the long term safety of advanced drugs that target the microvascular complications of diabetes.

Thank You