Developments in Diabetes
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Abstract:
Diabetes and its common precursor, the metabolic syndrome is becoming an epidemic worldwide and at an ever younger age. It is already the major precursor of death and will become dominant in deprived countries very soon.

All diseases are due to genomic predisposition and expressed due to interaction with lifestyle, particularly the thrifty genotype and diet. This affords a huge opportunity for prevention.

Advances in molecular medicine and the information explosion has resulted in better understanding of diabetes at the molecular level and the development of more effective agents.

Very recently bariatric surgery has been shown to cure established diabetes in more than 90% of patients.

Key Word: Diabetes, Diabesity

Introduction
Diabetes has been recognized for thousands of years and is generally viewed as a chronic medical condition with an inexorable course associated with multiple life threatening complications that interfere significantly with quality of life.

Developments in Diabetes
Recent changes in population demography and advances in molecular medicine genomics and therapeutics have altered this approach in a rapidly evolving manner. These changes will be dealt with under 3 headings - the epidemic of diabesity, the cause and pathophysiology of diabetes and management.

1. The Epidemic of Diabesity:
The vast majority of diabetes are of the adult onset insulin resistant type and these are increasing at an alarming rate. It is expected that more than 50% of the population of developed countries will be obese within 20 years and of these 40-60% will become type 2 diabetics. Of more importance is that already more than 50% of death in the Arab world are due to chronic diseases. Pakistan has a 50% higher prevalence than its neighbour India and worryingly more than 20% of deprived largely rural people are obese.

2. Cause and Pathophysiology:
The disease in the western world is clearly a disease of affluence and lifestyle and the epidemic is extending even to children. The root cause is thought to be thrifty genotype where the basic metabolism of our forefathers favoured fat storage for use in winter, famine and drought but which adapts very poorly to the modern lifestyle of plentiful energy dense food and a lack of physical activity leading to the thrifty phenotype and obesity.

Of perhaps equal importance is the realization that intrauterine programming, largely due to deprivation, is a precursor of adult diseases such as hypertension and diabetes 30-40 years later in adult life. Pakistan therefore has the worst of both worlds with an initial disease of deprivation complicated by a disease of dietary excess and sloth in childhood and adult life.

The genomic revolution has emphasized that all disease have a genetic component and more than 100 genes have been implicated as predisposing to type 2 diabetes. Whether diabetes develops in an individual depends upon a genetic interaction with the environment - largely diet and exercise.

This lays the ground for prevention or upstream management, which is far less costly and more effective than midstream interference (detection and management of high risk patients e.g. PCOS obesity, hyperlipidemia and the metabolic syndrome) and obviously streets ahead of downstream management of diabetes and its complications. The medical profession has competed ineffectively with the food industry in providing public awareness of long term prevention as opposed to immediate short term treatment of established disease.

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The pathophysiology of diabetes has evolved towards the realization that lipotoxicity\textsuperscript{10} is as important as glucotoxicity in diabetes with appreciation of the interaction between insulin and leptin, the adipostat\textsuperscript{11}. The fat organ clearly is metabolically and endocrinologically very active and the newly developed oral glitazones actually have maturation of fat cells as their major metabolic effects\textsuperscript{12}.

The multiple metabolic perturbations of diabetes, particularly the inflammatory process\textsuperscript{13} has resulted in multimodal treatment of diabetes with such agents as platelet inhibitors, statins and ACE inhibitors at an early stage of the disease.

A continuing problem is the gradual destruction of B cells which usually necessitates later insulin use despite continuing peripheral insulin resistance. Obvious candidates are insulin itself, AGES, the inflammatory process and triglycerides\textsuperscript{14}.

Management

1. Upstream Prevention

This is of particular importance in Pakistan and starts prior to pregnancy with careful attention to nutrition and the quality of ovulation. Management during pregnancy has also seen a change as the increased maternal insulin resistance is designed to assist the placental pump of glucose to the fetus. Using insulin as the primary management of gestational diabetes has a very limited effect on the incidence of large babies\textsuperscript{15} (and hence later adult diabetes) because it primarily treats the mother but the fetus only indirectly. Oral agents such as metformin, unlike insulin, cross the placental barrier and hence treats the fetus. A growing literature attests to an improved fetal outcome, with the original fear of fetal abnormalities having been discounted, even by the originators\textsuperscript{16,17}.

If reproduction is not an issue, lifestyle management has a major effect on subsequent development of diabetes. This entails exercise and a healthy diet. With regard to a healthy diet, the important factor is reduced intake in a manner that produces a sustainable lifestyle\textsuperscript{18}. The easiest manner is simply to reduce intake by 400 - 600 KCals by leaving 10 - 15% of everything that is eaten or drunk. This has replaced the complicated diets of the past. The constituents of the diet i.e. low fat or low carbohydrates, although of critical importance in established diabetes, are less important in prevention - the quantity is the major factor.

2. Midstream Prevention

The recognition of a family history is important in Pakistan and the metabolic syndrome is a major warning of danger ahead. It should be realized that, although there are several definitions, the clinical feature of abdominal girth (<100 cms in males and 88 cms in females) is a major give away in Pakistan as is hyper-triglyceridemia\textsuperscript{19}. Other major warnings are polycystic ovaries and there is no such entity as puppy fat in an adolescent. The blood sugar will be normal during insulin resistance and it is important to realize that a fasting insulin level in the upper quartile of the NORMAL range indicates insulin resistance (≥12 of the usual ELISA Kits). This, together with hypertriglyceridemia (≥150mg%) is the best screening test in suspicious circumstances, although lifestyle modification should be advocated even without biochemical confirmation, as in polycystic ovarian disease. The widely used stratagem of simply losing weight in PCOS, totally misses the consequences of insulin resistance in Pakistan as well as having a high reproductive failure rate.

3. Downstream Management

Strict control of diabetes, hypertension and assessment of complications are very important although limited improvement can be expected in established disease\textsuperscript{20}. Fifty percent of diabetes are diagnosed subsequent to myocardial infarction and Glucose : insulin and potassium has been shown to significantly improve outcome in the acute stage\textsuperscript{21}.

Oral agents, as a result of molecular medicine advances, are burgeoning. At present, the glitazones\textsuperscript{22} (pioglitazone and resiglitazone) appear to be the most effective, often combined with insulin.

Insulin delivery systems have been improved, particularly insulin gargline and the soon to be introduced nasal insulin\textsuperscript{23}.

The major advances in cure of diabetes have been two fold. The Canadian use of instillation of β cells into the portal veins has had some success but is costly and long term results are doubtful\textsuperscript{24}. Far more importantly, bariatric surgery with diversion of upper G.I.T secretions to the lower ileum has resulted in CURE of diabetes in 83 - 100% of patients. This has been confirmed in multiple series\textsuperscript{25,26}. We therefore need to modify our theories of the etiology of diabetes\textsuperscript{27} as well as our perception that it is not curable, while concentrating on prevention.

References


6. Hales CN and Barker DJ. The thrifty phenotype Hypothesis. British Medical Bulletin. 60 5-20.


