New Approaches in the Management of Non-insulin Dependent Diabetes Mellitus

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Epidemiological studies carried out in India have brought into focus, the high prevalence of non-insulin dependent diabetes mellitus (NIDDM) in our population. The studies have also shown that both the urban and the rural populations who have not yet developed diabetes have a high potential to ultimately develop NIDDM. Specific variations in the clinical profile are seen in the Indian population particularly with respect to the low age of onset of NIDDM.

Extensive family studies have indicated the important role played by hereditary factors in the aetiopathogenesis of NIDDM. Follow-up studies of prediabetic individuals, genetically prone to develop the disease, have shown that these individuals show several early stages of minor degrees of glucose intolerance with a high risk of progression to overt clinical diabetes. Definite biochemical abnormalities in the secretion and action of insulin are also seen which can serve as early biochemical markers in the natural history of the development of NIDDM.

Though a genetically determined disorder, NIDDM has a long period of latency prior to the development of clinical signs and symptoms. This period can be utilized to institute preventive measures. The need of the hour is a drastic change in our approach to the management of NIDDM with more emphasis on the preventive aspects to effectively tackle this major public health problem.

INTRODUCTION

The problem of diabetes mellitus has assumed great significance in our country. Our epidemiological studies have brought into focus the increasing prevalence of diabetes and hence the burden caused on the society by diabetes in India. A recent survey conducted by the Diabetes Research Centre, Madras (1) comparing a rural and an urban population near Madras city has shown a high prevalence rate of 8.2% in the urban area and a lower rate of 2.3% in the rural area. Interestingly, the study also showed that nearly 8% of the population in both the rural and urban areas had impaired glucose tolerance (IGT) indicating their high potential to ultimately develop diabetes. These figures could mean that there will be about 40 million subjects with diabetes by the turn of the century, thus posing a major public health problem in this country.

Pecularities of Diabetes in Indians

Studies carried at the Diabetes Research Centre, Madras, during the last three decades have shown specific variations in the clinical profile of diabetes as seen in India when compared with that seen in western countries. These variations include (a) a lower prevalence of insulin dependent diabetes mellitus (IDDM) in comparison to the western countries; (b) special characteristics seen in the non-insulin dependent diabetic (NIDDM) patients (2, 3) and (c) the presence of malnutrition related diabetes mellitus (MRDM).

Non-insulin dependent diabetes mellitus constitutes more than 96% of the total diabetic populations and the age at diagnosis of NIDDM in our patients occurs a decade or two earlier than that seen in western countries. 38% of our NIDDM patients have age at onset of NIDDM less than 40 years and about 5% have onset below 25 years. There is a predominance of males in our patient population and majorities (80%) of them are not obese. Hereditary factors seem to play a very important role in the aetiopathogenesis of NIDDM in Indian patients.

Strateries of Management of NIDDM

Presently, the situation appears to be that clinicians are satisfied with running clinics where patients report to them after the onset of clinical diabetes with symptoms and very often with complications. A lot of time, energy and resources are spent to establish centres of excellence equipped with facilities to look after the various complications of diabetes. While there is no doubt regarding the necessity and the utility of these procedures, it must be emphasized that in the management of NIDDM, there is an urgent need to bring in a new approach and help the diabetic to live a longer and fuller life.

To succeed in this mission, it is not sufficient if we only achieve metabolic and clinical control

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after symptoms have set in. Steps should be taken to prevent or delay the onset of the vascular changes. For this, our efforts must start quite early in the life of an individual, who is prone to develop clinical NIDDM. So far, neither the public nor the authorities concerned have taken this very important public health problem seriously.

Evolution of NIDDM - influence of hereditary Factors

Despite being a multifactorial disease, there are two main factors, which are important in the causation of NIDDM, namely the genetic and the environmental factors. It is obvious that while the genetic factor cannot be modified ater birth, the environmental factors could be influenced to a great extent. Several factors which are known to predispose to diabetes in a susceptible population are a) obesity b) excessive intake of calories and free sugar c) lack of physical activity d) infections e) extreme conditions of physical and emotional stress f) increased parity and g) diabetogenic drugs. Amongst these, heredity is of course the most important factor.

Extensive family studies carried out during the last three decades at the Diabetes Research Centre, Madras, have brought in ample supportive evidence in favour of this concept of evolution of diabetes which was based on very little evidence at the time of its proposal as early as in 1964. The strong familial aggregation noted in our NIDDM patients (4) and our long experience in the study of the natural history of diabetes has shown that one could identify the high-risk group of young individuals from a detailed analysis of their family history, screen them for carbohydrate intolerance and follow them up for several years.

For this purpose, family registries have been established in which all details regarding the parents and offspring in the families are carefully recorded and maintained for further analysis. Currently, details of 9,090 families with both parents diabetic and 17, 465 families with one diabetic parent are being maintained and continuously updated at the Diabetes Research Centre, Madras.

Our studies on the influences of the degree of the family history on the prevalence of diabetes in the offspring have yielded very interesting data. The prevalence of NIDDM among offspring of conjugal diabetic parents (OCDP) was 62% (diabetes 50% and IGT 12%)- the highest reported so far for any population. The offspring develop diabetes at a younger age compared to the parents. In subsequent study, it was noted that 88.8% of OCDP has already become diabetic by the age of 50 years. It was further estimated that 99% are likely to develop diabetes by the age of 65 years.

The prevalence of diabetes was 34% in offspring of one diabetic parent and 54% in offspring who in addition to a diabetic parent had a first-degree family history on the non-diabetic parental side (5). When 64 OCDP, who were normoglycaemic initially, were retested after a mean period of 5 years (range 4-9 years), 15.6% had developed diabetes, 29.7% showed IGT and the remaining 54.7% had maintained normal glucose tolerance. A cross-sectional analysis of the family history of our patient population showed an overall prevalence rate of 62% which could be attributed to a prevalence rate of 43% in parents, 10% in first degree relatives and 9% in second degree relatives. Such a high rate of prevalence of diabetes is a significant finding in the family history of our NIDDM population. Thus, the data from our family studies have very clearly brought out the important role played by the hereditary factor in the development of NIDDM in our patient population.

Studies on the natural history of diabetes - Follow-up of pre-diabetic individuals

In 1954 Conn and Fajans introduced the cortisone augmented glucose tolerance test (CAGTT) as an investigative aid in the effort to identify potential diabetes before the disease became evident by standard tests. A study carried out by us on healthy young relatives of diabetic patients attending the clinic revealed very interesting results. Out of the 104 subjects with diabetic relatives studied, 34 were found to be positive reactors to CAGTT. None of the 15 control subjects (with no diabetic relatives) showed a positive response in the CAGTT. We were able to recall 16 of the 34 CAGTT positive reactors for a follow-up study. The follow-up period varied from 24 to a maximum of 34 years. During this period, 12 out of the 16 individual followed-up developed overt diabetes. Obesity, infections, repeated pregnancies and improper diet were identified as the precipitating factors in these 12 individuals who developed diabetes. The results of this unique prospective study extending over 34 years gave us an insight into the natural history of the evolution of NIDDM and helped us to understand the natural progression of NIDDM and the important factors influencing it (6).

Since the diabetic gene is inherited by the offspring from the diabetic parents at the time of conception, the pre-diabetic state may be regarded as existing from conception to the time of detection by standard methods. At the Diabetes Research Centre, Madras, we have observed that some individuals show only minor abnormalities of glucose intolerance such as a raised peak in the oral GTT. These cannot be classified as IGT but could be considered as showing early glucose intolerance (EGI). Among Indians who have a strong family history of diabetes it has been observed that more importance has to be given even to minor degrees of glucose intolerance due to the very high risk of progression of these individuals to IGT and further to overt clinical diabetes.

We have been able to demonstrate a still earlier stage in the natural history of NIDDM in which an abnormal glucose tolerance test may be observed only under stress as shown by CAGTT. A classical example of this is the glucose intolerance seen during pregnancy (gestational diabetes). In our recent studies, we have been able to show changes in the hormonal profile (insulin/C-peptide ratio) even when glucose tolerance was perfectly normal.

Early Biochemical Abnormalities in the Pre-diabetic state

Non-insulin dependent diabetes mellitus is a disorder characterized by defective insulin secretion and action and has a strong genetic basis. It is possible that these abnormalities may precede the development of carbohydrate intolerance. Because of high risk of developing NIDDM adult OCDP are the ideal subjects in whom early abnormalities of insulin sensitivity are likely to be seen.

Our studies in OCDP have demonstrated higher serum insulin responses during an oral GTT (7) and a diminished first phase release of insulin during intravenous GTT (8). Studies on genetically predisposed families have suggested that in many instances insulin resistance was indeed present before diabetes developed, and that the insulin resistance and relative insulin deficiency could be attributed to a combination of receptor and post-receptor defects. Direct evidences for the presence of insulin resistance in OCDP have been obtained by the measurement of insulin sensitivity (7) and by studies on insulin bindings to its receptors (9).

Our initial work on OCDP has shown that it may be possible to influence the abnormalities in the first phase insulin response seen in these subjects by instituting appropriate measures. Very encouraging results have been obtained and this has proved to be a very important step in the prevention of clinical diabetes.

Summarizing our findings, it could be said that definite biochemical abnormalities in the secretion and action of insulin have been demonstrated in individuals who are genetically predisposed to diabetes. These abnormalities are probably determined by the genetic background and may serve as early biochemical markers in the natural history of the development of NIDDM.

Strategy for Primary Prevention of NIDDM

Although NIDDM is a genetically determined disorder, it has a long period of latency during which the regulatory mechanisms resist the forces working for unmasking of clinical diabetes. Definite biochemical abnormalities can be made out many years prior to the development of clinical signs and symptoms. This long period of latency could be utilised to institute some preventive measures as shown below:

i. Though genetic counselling is one of the accepted methods of prevention of any hereditary disorder, it has not got into practice in the case of diabetes due to lack of knowledge of exact genetic mechanisms of diabetes.

ii. Identification of high-risk groups is very important. The search for hidden diabetes becomes successful when more families with diabetes are tested not only once but also periodically.

iii. Correction or prevention of the environmental (diabetogenic) factors.

iv. Biochemical abnormalities have to be detected in genetic pre-diabetics early in the life of these individuals by proper screening and steps should be taken to institute corrective measures.

v. Regular follow-up and constant motivation is required to ensure that these preventive measures are put into practice over a number of years. Education imparted to diabetics, their families and the community at large goes a long way in achieving this goal.

CONCLUSION

An inexplicable inertia exists today in accepting NIDDM as a preventable disease though many other chronic diseases have already been submitted to effective prevention regimen. The need of the hour is drastic change in our approach to the management of NIDDM with more emphasis on the preventive aspects for the benefit of posterity.

REFERENCES

1. Ramchandran A, Snehalatha C, Dharmaraj D, Vishwanathan M. Prevalence of glucose intolerance in Asian Indians-Urban-rural difference and significance of upper body adiposity. Diabetes Care 1992 (in press).

2. Mohan V, Ramachandran A, Snehalatha C, Mohan R, Bharani G, Vishwanathan M, High prevalence of maturity onset diabetes of the young (MODY) among Indians. Diabetes Care 1985; 8: 371-4.

3. Viswanathan M, Vijay V, Ramchandran A, Mohan V. Observations of NIDDM in India. In world Book of Diabetes in Practise Krall LP, (Ed.) Vol. 3 Elsevier 1988; p 37-40.

4. Viswanathan M, Mohan V, Snehalatha C, Ramchandran A. High prevalence of Type 2 (non-insulin dependent) diabetes among offspring of conjugal diabetic parents in India. Diabetologia 1985; 28: 907-10.

5. Ramachandran A, Mohan V, Snehalatha C, Viswanathan M. Prevalence of Non-insulin dependent diabetes mellitus in Asian Indian families with single diabetic parent. Diab. Res. Clin. Pract. 19878; 4: 241-5.

6. Viswanathan M. Prevention in diabetes. J Assoc. Phys. India 1981; 29: 251-61.

7. Ramachandran A, Snehalatha C, Mohan V, Bhattacharyya PK, Viswanathan M. Decreased insulin sensitivity in offspring whose parents both have Type 2 diabetes. Diabetic Med. 1990; 7: 331-4.

8. Ramachandran A, Snehalatha C, Mohan V, Vishwanathan M. abnormalities in insulin response to intravenous glucose in offspring of conjugal (Type 2) diabetic parents. J Assoc. Phys. India 1990; 38: 265-7.

9. Ramachandran A, Susheela L, Mohan V, Kuzhali DAS, Viswanathan M. Abnormalities in erythrocyte insulin binding in offspring of conjugal non-insulin dependent diabetic parents. Diab. Res. Clin. Pract. 1988; 5: 241-7.