Aetiopathogenesis of Type - 2 Diabetes Mellitus: Could Chronic Stress Play an Important Role?

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Abstract

Objectives: Pathogenesis of type-2 diabetes remains elusive. Various factors including diet, physical exercise, obesity, genetic factors and stress, have been discussed. Among these factors role of stress is still poorly understood in diabetes. Therefore the study was planned to assess effect of stress in diabetic and non-diabetic population in a comparative descriptive manner.

Methods: 1000 diabetic cases (group A) and equal number of healthy individuals were selected as a comparison group (group B). Both groups were examined at 0, 12, 24 months. To assess stress 17 points were examined (factors mainly related to emotions, hurriedness, relaxed status etc.), total 68 points for stress were given; > 30/68 was considered as severe stress. Mental health life style factors like duration of sleep and working mental hours were also examined. EEG and SSR were done at 24 months to assess stress and sympathetic response.

Results: There was presence of chronic stress, (> 90% had > 30/68 scoring) more mental work and less sleep duration in group A. EEG showed synchronised v/s desynchronised basal rhythm in group B v/s group A. SSR suggestive of increased sympathetic activity in group A.

Conclusion: It is concluded that chronic stress leads to increased basal sympathetic activity, resulting from disturbed cortical hypothalamic axis, leading to central insulin resistance and diabetes.

Introduction

Pathogenesis of type-2 diabetes remains elusive. Primary events leading to/precipitating type 2 diabetes are largely unclear. Various studies have shown genetic defect, obesity, stress, dietary factors, and lack of physical activity are responsible for diabetes. All these are associated with insulin resistance, insulin secretory defect and diabetes. Among all these factors stress is poorly explored and understood; therefore the study was aimed to review stress in diabetic and non-diabetic people. Stress cannot be defined in a single word. According to Dorland’s medical Dictionary ‘stress is the sum of biological reactions to any adverse stimulus, physical, mental or emotional, internal or external that tend to disturb organisms homoeostasis’; so, all factors which could produce stress were examined.

Material and Methods

This is a descriptive longitudinal comparative study between diabetic and non-diabetic people, for assessing effect of stress on diabetes. 1000 cases (group A) and equal numbers of control (group B) were selected for study. Group A cases were selected from medical OPD of Mittal hospital and JLN Medical College Ajmer, Rajasthan, India. People in these hospitals come from around 100 kms. The city itself has a population of a million. The assessment was done at 0, 12, 24 months. The prevalence of diabetes in Rajasthan is 8.6% close to the National data 8%. Group B subjects were selected from Ajmer city (300) and (700) from villages within 30-40 kms of Ajmer. The
villages selected were Bhanwta, Picholiya, Budhwada (Pisangan Tehsil) and Gudda, Ladpura (Kishangarh). These villages supply vegetables, milk, and other farm produce to Ajmer, and environmental factors remain grossly similar in the city and these villages. The age group was 35-40 years in both groups. The duration of diabetes was one year or less than one year. Both groups were studied for 2 years. Both groups were equally matched according to age and sex. Cases having hypertension, cardiac and thyroid diseases were excluded from the study. The following factors were examined-

1. BMI, physical activity, family history, dietary calories at the beginning
2. Stress assessment at 0, 12, 24 months
3. Routine Examination (pulse, blood pressure in supine position, respiration) at 0, 12, 24 months
4. Special tests – EEG (16 channel), Electroencephalogram and SSR (Sympathetic skin response) (Recorders and Medicare systems) assessed at 24 months.

Stress assessment: This was done in 2 parts. Firstly, subjective recording of day to day mental health lifestyle factors which could lead to stress and diabetes; and secondly objective examination of stress through a scale, with the help of a normalised questionnaire, mainly based on perceived stress scale (PSS) (total 17 points; each having score of 0-4).

Subjective Recording

1. Working hours of mental activity (Duration <> 7 Hrs.) Mental activity included all work which involves active mental involvement and affects mental health (Reading, Writing, and Office Work, computer/ laptop/ TV etc.).
2. Mental rest (week end/ month end/ no clear rest), when no active participation in mental work is there i.e. rest on Sundays, going for picnic etc.
3. Sleep duration (< 7 Hrs.)
4. Duration of presence of above habits (< 5 years, chronic > 5 years).

Objective assessment

Following factors were analysed through a questionnaire based mainly on PSS with rating 0, 1, 2, 3 or 4 which indicates severity; 0 = never, 1 = almost never, 2 = sometimes, 3 = fairly often, 4 = very often (total 17 items/ points in stress with maximum score of 68; Normal range 0-16, mild stress 17-20, moderate 21-30, severe > 30/68).

1. Attached with anxiety; anticipates the worst, repeatedly asks about the wellness at workplace/ relatives
2. Tension- restlessness, trembling
3. Flow/crowding of ideas (Much/ Less)
4. Attached/hooked with ideas (Short Duration \ Long Duration)
5. Loss of Control (easy \ not easy). (Factors 3, 4, 5 are related to emotions)
6. Mental speed/hurriedness- Time taken in eating food (adequate 15 minutes, inadequate < 15 minutes) (hurriedly/ relaxed way), picking up phone calls quickly, every time trying to complete work in a short period (in haste)
7. Sleep Pattern (insomnia) (Sound \ Frequent Awakening)
8. Intellectual- Poor concentration, memory, decision making ability
9. Presence/absence of ease/freeness in mind
10. Ability/ inability to divert mind
11. Sense of enjoyment (Factors 9, 10, 11 are related to relaxed state)
12. High expectation
13. Jealousy
14. Competitiveness
15. Feeling of self confidence
16. Depressed mood- decreased interest in work
17. Mental fatigue

Patients were assessed throughout questioning (behaviour, talkativeness, speed of eating rough assessment of hurriedness/mental speed). Cross questioning was done at times. Small groups were examined by a single examiner. The objectivity of memory was assessed by repeating the first question in the end i.e. what was asked in the beginning.

EEG- EEG was done on a 16 channel system in a dark silent room. Eye closure, eye opening and other activating methods photic, and hyperventilation was done.

SSR –SSR was done with standard protocol in supine, relaxed, semi darkened room with ambient temperature control at 22-24°c in the upper limbs. Skin temperature was constantly measured if < 22°c the limbs were warmed. In this process, standard surface electromyography disc electrodes were applied with conducting paste to the palm and dorsum of the hand, with a reference electrode on the forearm. Hand grip, cold pressor, loud voice and hyperventilation were used as provocative methods. Skin potential changes during and between the tests were analysed by a computer. Latency was measured from the onset of stimulus artifact to the beginning of response. Amplitude was recorded peak to peak.

Results

There was no major difference in vital parameters, physical activity and dietary calories (Table 1).
Family history was positive in 35% cases of group A; whereas only 2% in group B. In group A, subjective assessment was suggestive of more mental working hours and less sleep as compared to group B. Stress assessment score > 30/68 was present in 90% of group A as compared to 4-5% in group B (Tables 2, 3).

In EEG group B had synchronised Alpha/Theta basal rhythm as compared to desynchronised low voltage Beta in group A (Table 4).

SSR- There was high voltage spike response in group A as compared to flat dome shaped response in group B (Table 4).

Discussion

Type 2 diabetes is a multifactor disease. Dietary,
In general examination the average BMI in Group A was 24 kg/m² as compared to 22 kg/m² in Group B. Despite the difference, the BMI in both groups was within normal limits (non-obese/18-24.9 kg/m²) (Table 1). Among vital parameters there was no major difference in resting pulse rate, respiratory rate and blood pressure (Table 1).

In physical activity group A, 84% cases had good activity schedule (at least 30 minutes daily for 5 days a week) as compared to 91% in group B (Table 1).

In genetic factors positive family history was 35% v/s 2% in group A v/s group B (Table 1). Average calorie intake was 1900-2100 Kcal in group A v/s 1800-2000 in group B.

Stress is considered to precipitate diabetes in some studies.³,⁴ In subjective day to day mental health assessment, in group A > 7 hours of mental working was present in 85% of cases as compared to 10% in group B, mental rest at week end was only 15% in group A v/s 75% in group B; short duration of sleep was 92% v/s 16% in group A v/s group B. All these habits were present in > 90% for more than 5 years in almost both the groups. All these features suggest excess mental work and less mental rest in group A. Chronicity of all these factors make person prone to develop stress and diabetes.⁸,⁹

In objective assessment, group A had score > 30/68 (severe stress) in 90% as compared to 10% in group B at 0 month (Table 3). There was no gross change after 12 and 24 months. Group A cases had multiple reasons to develop stress including crowding of ideas, always attached/hooked with ideas, jealousy, competitiveness, inability to divert mind, hurriedness, mental fatigue etc. Group A cases were found to be chronically stressed due to emotional/social reasons (present for > 24 months) (Table 3), and inappropriate day- to- day mental health life style factors (present for > 5 years) (Table 2). Chronic stress is defined as the response to emotional pressure suffered, for a prolonged period, over which an individual perceives that he or she has no control. If this continues for a long time, it can cause damage to an individual’s physical and mental health.

### Table 4: EEG and SSR

<table>
<thead>
<tr>
<th>SSР left upper limb</th>
<th>Group A</th>
<th>Group B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Response Prototype</td>
<td></td>
<td></td>
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<tr>
<td>Average Latency sec</td>
<td>0.07</td>
<td>0.7</td>
</tr>
<tr>
<td>Voltage (peak to peak) mV</td>
<td>10±0.8</td>
<td>2±0.7</td>
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<tr>
<td>Hand grip</td>
<td></td>
<td></td>
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<tr>
<td>Latency sec</td>
<td>0.07</td>
<td>0.8</td>
</tr>
<tr>
<td>Voltage mV</td>
<td>11±1.04</td>
<td>3±0.8</td>
</tr>
<tr>
<td>Cold pressor test</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Latency sec</td>
<td>0.07</td>
<td>0.8</td>
</tr>
<tr>
<td>Voltage mV</td>
<td>9±0.9</td>
<td>2±0.7</td>
</tr>
<tr>
<td>Clap sound/loud voice</td>
<td>0.08</td>
<td>0.8</td>
</tr>
<tr>
<td>Voltage mV</td>
<td>9±0.9</td>
<td>2±0.7</td>
</tr>
<tr>
<td>Hyperventilation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Latency sec</td>
<td>0.8</td>
<td>0.9</td>
</tr>
<tr>
<td>Voltage mV</td>
<td>4±0.7</td>
<td>3±0.6</td>
</tr>
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EEG (Basal Rhythm)

<table>
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<tr>
<th>Leads T5-01 longitudinal</th>
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<tr>
<td>40% High voltage Beta</td>
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<tr>
<td>60% Low Voltage fast Beta</td>
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EEG (After photic stimulation)

<table>
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<tr>
<th>Frontal rhythm FP2-F4 Longitudinal</th>
</tr>
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<tbody>
<tr>
<td>90%</td>
</tr>
<tr>
<td>70%</td>
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<tr>
<td>10%</td>
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</tbody>
</table>
There were few differences in EEG in both groups. Firstly low voltage beta (60%) and high voltage beta (40%) activity as basal rhythm in group A (desynchronised EEG), as compared to Alpha (60%)/ theta (20%)/ high voltage beta (20%) as basal rhythm in group B (synchronised EEG); secondly presence of low voltage beta in frontal leads (90%) in group A v/s Alpha (70%)/theta (10%)/ high voltage beta (20%) in group B; thirdly basal rhythm doesn’t get disturbed with photic stimulation (group B) as compared to disturbance/further desynchronisation in basal rhythm in group A; i.e. low voltage beta after such stimulus(either already existing or gets converted into low voltage beta).

Basal alpha/theta activity suggests a state of synchronisation.\(^{13}\) Alpha associated with awake rest, and Theta with awake extreme relaxation/drowsiness.\(^{14,15}\) In this study, group B cases have such EEG findings (Table 5).

Beta activity (desynchronised activity) is a state of mental work\(^{16}\) and low voltage beta is a state of further desynchronization\(^{17}\) i.e. state of extreme mental work or stress.\(^{18}\) In this study the chronically stressed patients of group A have similar EEG findings.

In sympathetic skin response (SSR) there was short latency and spike response in group A, as compared to long latency, low amplitude, domelike response in group B. Average amplitude after stimulation by hand grip, cold immersion and loud voice was (10 mV, 11 mV and 9 mV as compared to 2 mV, 3mV and 2 mV in group B (Table 4). Values were almost similar in both groups after hyperventilation. Previous studies\(^{11,12}\) have found increased amplitude and short latency in cases with high sympathetic activity.

The present study clearly indicates three findings in group A. First the presence of chronic stress (suggested by questionnaire and EEG changes); Second increased basal sympathetic activity [(suggested by SSR) (There is no overt increase in sympathetic activity because resting pulse rate is normal)] (Table 1). Third is the presence of diabetes.

This relation between stress and diabetes is complex. The possible mechanism seems to be the following:

Cerebral cortex has extensive connections with hypothalamus;\(^{18}\) hypothalamus receives afferent from limbic system (cingulate gyrus) neocortex and other areas (Figure 1). The hypothalamus (dorsomedial nuclei and lateral hypothalamic area) gives efferent to preganglionic sympathetic and parasympathetic neurons via reticulospinal tract; reaches to intermediolateral column of spinal cord (ends on cell body).\(^{18}\) From here, postganglionic sympathetic fibres arise from thoraco lumbar (T1-L2) area of spinal cord. Thus, cortex has some indirect control (modulating effect over hypothalamus) over sympathetic nervous system. Therefore, it appears that chronic stress results in impaired cortical-hypothalamic signals. Impaired hypothalamic signals lead to increased preganglionic and therefore increased postganglionic basal sympathetic rhythm. Increase in sympathetic\(^{15}\) activity is initially associated with insulin resistance in liver and muscle (mediated
via alpha 1 receptors)\(^{19}\) and later on inhibition of insulin release from pancreas (mediated via alpha 2 receptors) and diabetes\(^{20}\) (Flow chart 1).

### Conclusion

On the basis of the findings above, we conclude that chronic stress and defective daily mental health life style factors are directly related to diabetes. Therefore a hypothesis is made that chronic stress and impaired life style factors (especially more mental work and less mental rest) are important risk factors for initiating/precipitating diabetes.

### Acknowledgement

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### References


