A cross-sectional study on the role of stress in hyperglycemia and the effect of Mahatiktaka Kashaya (an Ayurvedic formulation) in its management

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Abstract

Background: Stress is a potential contributor to chronic hyperglycemia. Pitta Prakriti (body constitution) individuals are more prone to stress and the prevalence of type 2 diabetes in stressed out individuals is much more. Aim of study was to evaluate the role of stress in hyperglycemia in individuals of Pitta predominant constitution and to assess the effectiveness of Mahatiktaka Kashaya in stress-induced hyperglycemia.

Methodology: A cross-sectional study was carried out in 100 Pitta predominant patients having fasting blood sugar level greater than 140 mg/dl, to find the association of stress and hyperglycemia, using International Stress Management Association questionnaire followed by open labelled clinical trial with Mahatiktaka Kashaya (Decoction). Trial drug was administered at a dose of 15 ml twice daily for 14 days. Assessment was done before and after the treatment. Observation and Analysis: 80% of Pitta predominant individuals have reported stress-associated hyperglycemia. Overall effect of Mahatiktaka Kashaya in major domains of Stress Assessment Questionnaire, i.e., symptoms, stability and strategies was significant. Furthermore, the trial drug showed significant improvement in biochemical parameters of diabetes. Conclusion: The study concludes that there is significant association between stress and hyperglycemia in the individuals of Pitta constitution. Mahatiktaka Kashaya is found to be highly significant in stress-associated hyperglycemia in the above said group.

Keywords: Hyperglycemia, Mahatiktaka Kashaya, Prakriti, Prameha, stress, type 2 Diabetes

Introduction

“Stress” can be defined as any situation which tends to disturb the equilibrium between a living organism and its environment.[1] Stress is a part of life and is necessary for providing challenge to physiological and psychological development. However, too much stress over a period of time combined with poor coping habits may cause physical, chemical and hormonal imbalances in the body, thus leading to disease and death if left unchecked.[2] Stressors can be divided into two categories, external and internal causes. Family and relationship stressors, work stressors, etc., come under external causes and factors such as uncertainty or worries, low self esteem, self criticism, excessive anger and unrealistic expectations come under internal causes.[3] Stress is a potential contributor to chronic hyperglycemia in Madhumeha (type 2 diabetes). Exposure to stress stimulates the hypothalamic–pituitary–adrenocortical (HPA) axis causing release of various hormones, resulting in elevated blood glucose level.[4] It has major effects on metabolic activity as well. Signs of stress can be defined at cognitive, emotional, physical or behavioral level.[5]

In ayurvedic classics, Prakriti (psychosomatic constitution) is the sum total of anatomical, physiological and psychological factors, which plays an important role in the prognosis of disease and response to the treatment. It is a genetically transmitted trait.[6] Pitta predominant constitutions are said to be more vulnerable to psychological stress.[7] The prevalence of type 2 diabetes in stressed individuals is 2.6% in males

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and 2.1% in females. Significantly larger proportion of type 2 diabetes individuals had severe stress scores (23.4% vs. 10%; \( P < 0.001 \)) compared to healthy controls.\[8\]

Mahatiktaka is a Ghrita Yoga (ghee-based formulation) mentioned in Kushtha Chikitsa.\[9\] In routine clinical practice also, the Kashaya (decoction) form of this formulation is found to be effective in Madhumeha, especially when associated with stress. Further, it is ideal to prescribe Kashaya form of any preparation for long-term usage, especially in Kleda (excretory portion of body fluids)-predominant clinical conditions. The Kashaya formulation ensures Kleda Shoshana (reduction of Kleda) by virtue of its inherent action of taste. Mahathiktaka Kashaya is also practised for long term effectively in major types of Kushtha (skin disorders) which is also a Kleda (liquid waste product) predominant disease. The Kashaya Yoga is found to be more cost-effective when compared with medicated Ghrita in routine clinical practice. Amalaki juice (Emblea officinalis Gaertn.) is the main ingredient in this formulation and is widely practiced for various mental illness. Details of the formulation are enlisted in Table 1.

As stress has a significant impact on hyperglycemia, it needs to be addressed. Very limited research works are carried out in relation to Prakriti-based treatment strategy. Hence, a cross-sectional study was planned in this background to find the association between stress and hyperglycemia in individuals of Pitta constitution. A clinical study was also conducted in this milieu to evaluate the effect of Mahatiktaka Kashaya in stress-associated hyperglycemia in Pitta-predominant constitution.

### Aims and objectives

1. To evaluate the role of stress in hyperglycemia in the individuals of Pitta-predominant constitution
2. To assess the effectiveness of Mahatiktaka Kashaya in stress-induced hyperglycemia.

### Methodology

Two types of study design were used in the current work. A cross-sectional study and an open clinical trial were conducted in patients visiting the outpatient department of Kayachikitsa, Vaidyaratnam P.S. Varier Ayurveda College, Kottakal, Kerala, India.

### Table 1: Ingredients of Mahatiktaka Kashaya

| Sanskrit name | Botanical name | Part used | Quantity |
|---------------|----------------|-----------|----------|
| Saptacchadha  | Alstonia scholaris Linn | Twaka (bark) | 1 part |
| Parpata       | Hedystis coryoxa Linn | Samoola (whole plant) | 1 part |
| Aravsgada     | Cassia fistula Linn | Twaka (bark) | 1 part |
| Katuki        | Picrorhiza kurrooa Royle ex Benth | Samoola (Whole plant) | 1 part |
| Vacha         | Acorus calamus Linn | Kanda (rhizome) | 1 part |
| Haritaki      | Terminalia chebula Retz | Phala Twaka (fruit pericarp) | 1 part |
| Alamaki       | Emblica officinalis Gaertn | Phala Twaka (fruit pericarp) | 2 part |
| Vhibitaki     | Terminalia bellirica Roxb | Phala Twaka (fruit pericarp) | 1 part |
| Padmakam      | Prunus poddum Franch | Kasha (stem) | 1 part |
| Patha         | Cycelea pellata Hook. Fil and Thoms | Kanda (rhizome) | 1 part |
| Haridra       | Curcuma longa Linn | Kanda (rhizome) | 1 part |
| Darvi         | Coscinium fenestrum (Gaertn) Colebr | Kasha (stem) | 1 part |
| Sariva        | Hemidesmus indicus Linn | Mula (roots) | 1 part |
| Shatavarri    | Asparagus racemosus Wild | Kandhal (rhizome) | 1 part |
| Patola        | Trichosanthes lobata Roxb | Patra (leaves) | 1 part |
| Bramhi        | Bacopa monnieri Linn | Samoola (Whole plant) | 1 part |
| Vishala       | Citrullus colocynthis Linn | Samoola (Whole plant) | 1 part |
| Pippali       | Piper longun Linn | Phala (fruits) | 1 part |
| Gajapippali   | Scindapus officinalis Schoott | Mula (roots) | 1 part |
| Nimba         | Azadirachta indica A. Juss | Twaka (bark) | 1 part |
| Chandana      | Santalum album Linn | Sara (heart wood) | 1 part |
| Yashimadhu    | Glycyrrhiza glabra Linn | Kasha (stem) | 1 part |
| Ashwattha     | Ficus religiosa Linn | Twaka (bark) | 1 part |
| Katuja        | Holarrhena antidysenterica Roxb | Twaka (bark) | 1 part |
| Guduchi       | Tinospora cordifolia Willd | Kasha (stem) | 1 part |
| Kiratatikta   | Swertia chirata Linn | Samoola (whole plant) | 1 part |
| Usira         | Vetiveria zizanioides Linn | Mula (roots) | 1 part |
| Vasa          | Adhatoda vascia Nees | Patra (leaves) | 1 part |
| Murva         | Andrographis paniculata Wall. Ex Nees | Mula (roots) | 1 part |
| Ativisha      | Aconitum heterophyllum wall | Kanda (rhizome) | 1 part |
| Musta         | Cyperus rotundus Linn | Samoola (whole plant) | 1 part |
| Duralabha     | Fagonia cretica Linn | Samoola (whole plant) | 1 part |
Cross-sectional study design
This was carried out to find the association of stress and hyperglycemia among Pitta-predominant individuals.

Sample size
One hundred patients (25–60 years age group).

Inclusion criteria
- Pitta-predominant individuals with fasting blood sugar (FBS) level above 140 mg/dl
- Age between 25–60 years irrespective of gender and religion
- With informed consent.

Exclusion criteria
Patients having psychiatric illness and undergoing antipsychiatric medication.

Survey tools
1. Specially formulated questionnaire for Prakriti analysis
   It includes 10 major characters of all the three constitutions
2. International Stress Management Association (ISMA) questionnaire.[10]

To calculate the stress score, ISMA questionnaire containing 25 questions was used. According to the symptoms present in the individuals, the score is given. The score above 14 is suggestive of stress and stress-related diseases.

Open labelled clinical trial
The trial drug Mahatiktaka Kashaya was given for 14 days in 30 patients. Assessment was done before and after the treatment. Total scores before and after the medication were statistically analyzed.

Study design – Open labelled randomized clinical trial.
Age group – 30–60 years.
Dose – 15 ml.
Administration – With 45 ml lukewarm water twice daily before food.

Investigations
- FBS
- Postprandial blood sugar (PPBS).

Inclusion criteria
- Patients having blood sugar level (FBS 140–200 mg/dl) fulfilling criteria for Pitta-predominant constitution after getting informed consent
- ISMA stress score >14
- Age between 30 and 60 years.

Exclusion criteria
- Patients having psychiatric illness and under antipsychiatric medications
- Gestational diabetes
- Juvenile diabetes
- FBS >200 mg/dl
- Pregnant and lactating women.

Assessment
1. Evaluation of stress through Stress Assessment Questionnaire (SAQ) before and after the treatment
2. Assessment of biochemical parameters like FBS and PPBS before and after the treatment.

Interpretation of the data
The outcome was measured, and data were statistically analyzed using student “t”-test with two-tailed paired sampling.

Ethical clearance – IEC/CL/06/12 dated 19/05/12.

Observation and analysis
Cross-sectional study
One hundred individuals of Pitta-dominant Doshika constitution were selected for the study. Of the 100 individuals, 55 had FBS in-between 140 and 160 mg/dl, 29 within the range 160–180 mg/dl and 16 within the range of 180–200 mg/dl of FBS. Majority of the individuals were having FBS in-between 140–160 mg/dl. Fifty-five percent had PPBS within the range 200–225 mg/dl, 20% within the range of 225–250 mg/dl, 14% within the range 250–275 mg/dl and 11% within the range of 275–300 mg/dl of PPBS, respectively. Of 100 people, 80% had ISMA stress score >14 and the remaining 20% had stress score <14.

Among 85% of total Pitta predominance Prakriti persons (with Pitta character ≥7), 18% were having FBS >170 and 67% were having FBS between 170 and 120. Among them, 76% were having stress score >14 and 9% <14. Forty-nine percent of the Pitta Prakriti with stress score ≥14 were having FBS ≥170 and 31% of Pitta Prakriti with stress score ≥14 were having FBS between 170 and 120 (mg/dl). In the present study, the association between stress and hyperglycemia and between Pitta Prakriti and hyperglycemia was calculated and a significant association was observed. 80% of Pitta-predominant individuals have reported stress-associated hyperglycemia [enlisted in Tables 2-4].

| Table 2: Association between Pitta Prakriti and fasting blood sugar level |
|-----------------------------------------------|
| FBS | Pitta character | Total | $\chi^2$ | $P$ |
|-----|-----------------|-------|----------|-----|
|     | >7 <7           |       |          |     |
| >170| 18 04           | 22    | 13.82    | <0.001 |
| <170| 67 11           | 78    | 10.82    | <0.001 |
| Total| 85 15           | 100   |          |     |

FBS: Fasting blood sugar

| Table 3: Association between stress and fasting blood sugar level |
|-----------------------------------------------|
| FBS | Pitta character | Total | $\chi^2$ | $P$ |
|-----|-----------------|-------|----------|-----|
|     | >7 <7           |       |          |     |
| >170| 49 04           | 53    | 10.82    | <0.001 |
| <170| 31 16           | 47    |          |     |
| Total| 80 20           | 100   |          |     |

FBS: Fasting blood sugar
Open labelled clinical trial
Effect of therapy showed significant result in biochemical values. 11.87% and 14.6% relief were observed in FBS and PPBS respectively [Table 5].

Overall effect in major domains of SAQ are 5.85% relief in symptoms, 4.76% improvement in stability and 16.34% improvement in strategies, respectively. Mean BT score was reduced from 21.21 to 19.96 with 5.85% relief. The improvement found in this domain is mainly due to the psychological counseling (psycho-education) given to the patient during the period of intervention [Tables 6, 7 and Graph 1].

Discussion
Stress and hyperglycemia
Role of stress in the onset of type 2 diabetes in individuals predisposed to diabetes and in blood glucose control in people with established diabetes is already proved. Activation of HPA axis causes release of increased amounts of glucocorticoids, in particular cortisol, enhances gluconeogenesis in the liver and diminishes cellular glucose uptake. It also leads to immunosuppression. Stress-induced release of growth hormone can also decrease glucose uptake and endorphin will suppress insulin secretion and elevate glucose levels. Therefore, stressful stimuli has impact on glucose levels through numerous pathways. Eventually, elevated blood glucose levels by themselves impair the ability of pancreas to respond to glucose stimulus. Stress management and progressive muscle relaxation have been shown to be very effective in the treatment of disorders with a psychophysiological component.

Discussion on demographic data
Cross-sectional study
Among 100 participants, majority of participants (48%) belong to 40–50 years of age group. Female participants accounts for 53% and male participants constitute 47% of survey population. Moreover, the prevalence of moderate stress was estimated to be highest in the 40–44 years age group. The major stress sources were parenting, relationship, incident and work. A significant association between stress and hyperglycemia was detected in individuals of Pitta constitution. Among the three types of constitution, Pitta Prakriti individuals are more prone to stress and other emotional disturbances, as they are described as Klesha Asashishnava (inability to face difficult situation) and Kshiprapapradasa (short tempered and easily delighted). Among various types of Pitta, mainly Saadhaka Pitta plays a role in immediate response and has a close association with the psychological functioning of

Table 4: Association of blood sugar level with Pitta Prakriti and stress

| Parameters       | Score (%) | FBS level (mg/dl) |
|------------------|-----------|-------------------|
| Pitta character >7 | 49        | ≥170              |
| Stress score >14  | 39        | 120-170           |

FBS: Fasting blood sugar

Table 5: Percentage of improvement in blood sugar level

| Parameters  | Mean score | SD     | Percentage of relief | t     | P     |
|-------------|------------|--------|----------------------|-------|-------|
| FBS         | 166.03     | 146.33 | 11.87                | 7.96  | <0.001|
| PPBS        | 232.43     | 199.17 | 14.3                 | 7.08  | <0.001|

BT: Before trial, AT: After trial, SD: Standard deviation, FBS: Fasting blood sugar, PPBS: Postprandial blood sugar

Table 6: Effects of Mahatiktaka Kashaya in major domains of stress assessment questionnaire

| Parameters       | Mean score | SD     | Percentage of relief | t     | P     |
|------------------|------------|--------|----------------------|-------|-------|
| Symptoms         |            |        |                      |       |       |
| Emotion          | 6.83       | 5.4    | 12.2                 | 20.94 | 6.42  | <0.001|
| Behavior         | 7.16       | 5.20   | 0.99                 | 27.45 | 10.78 | <0.001|
| Physical         | 7.33       | 5.57   | 0.89                 | 24.11 | 10.78 | <0.001|
| Stability        |            |        |                      |       |       |
| Procrastination  | 7.06       | 5.73   | 1.09                 | 17.5  | 6.68  | <0.001|
| Perfectionism    | 6.73       | 5.53   | 1.09                 | 17.83 | 6     | <0.001|
| Self-esteem      | 7.27       | 5.8    | 0.89                 | 7.27  | 7.07  | <0.001|
| Depression       | 7.43       | 5.46   | 0.85                 | 26.47 | 12.69 | <0.001|
| Anxiety          | 7.43       | 5.57   | 1.07                 | 25.12 | 9.52  | <0.001|
| Strategies       |            |        |                      |       |       |
| Social support   | 4.06       | 6      | 1.46                 | 47.89 | 7.25  | <0.001|
| Self-regulation  | 4.28       | 5.93   | 1.24                 | 39.06 | 7.36  | <0.001|
| Problem-solving  | 4.57       | 6.53   | 1.33                 | 43.07 | 8.12  | <0.001|
| Distraction      | 4.27       | 6.27   | 1.44                 | 46.87 | 7.61  | <0.001|
| Health           | 4.7        | 7.7    | 1.8                  | 63.83 | 9.12  | <0.001|

BT: Before trial, AT: After trial, SD: Standard deviation

Graph 1: Percentage relief of domains in SAQ (in open trial)
the body.[17] Moreover, in the etiopathogenesis of Paññitika Prameha, involvement of Santapa (grief), Shrama (exertion) and Krodha (anger) are explained.[18] Anger, particularly anger temperament, is associated with the onset of type 2 diabetes. Due to the abovesaid reasons, Sadhaka Pitta gets vitiated very faster, which is directly connected with the formation of Ojas and leads to Ojakshaya. In this situation, the person cannot respond appropriately to a given situation, named stress. Continuous stress alters the quality of Apara Ojas (innate immunity). This will result in the faster manifestation of Pittaja Prameha (stress diabetes) due to Ashukaritwa (rapid action) of Pitta.[19]

Clinical trial

Maximum number of patients were in 40–50 years age group. 100% of participants reported fluctuating FBS level and 80% were free from family history of diabetes. 70% had unhealthy food habits and low exercise levels. Mahatiktakakashaya is found to be highly significant in stress-associated hyperglycemia in Pitta constitution. Mahatiktaka Gritha is effective in various ailments including Unmaada (insanity), Apasmara (epilepsy), Kashtha (skin disease), Hridroga (heart disease), and in all Pitta Vikaara (disorders due to imbalance in Pitta Dosha). This is widely practiced for psychological conditions as well. In a dissertation study on the efficacy of Mahatiktaka Gritha in Krodha (anger) with special reference to Pittiik Unmaada (insanity), significant effect was noticed.[20] As the current work is on Madhumeha, it is better to administer the above Yoga in Kashaya form. In Madhumeha (Prameha) where the patient is not suitable for Shodhana (purification), Shamana chikitsa (pacification), in the form of Kashaya or Mantha can be administered.[21] Hence, Mahatiktaka Gritha formulation was modified to Kashaya Kalpana and administered. As the Yoga has Sheeta (cold) and Kleda Shoshhana (obserption of waste liquid) property, it can alleviate the Ushna (hot in potency) and Tikshna Gunavriddhi (penetrating property) of Pitta. Furthermore, while addressing the Pitta Kopa (vitiation of Pitta) the correction of Dravarupa Pitta Vriddh (increased state of Pitta) is met along with Kledasamaavastha. Further Samprapti leading to the development of hyperglycemia can be arrested by normal functioning of Saadhaka Pitta and Ojas.

Conclusion

In this current era, stress has a key role in the etiopathogenesis of diabetes. The present study proves that hyperglycemia which occurs in individuals of Pitta constitution is primarily stress induced. Furthermore, the effectiveness of the trial drug “Mahatiktaka” which is indicated in mental disorders is highly significant in stress-associated hyperglycemia in Pitta constitution. This shows the importance of stress evaluation while treating a diabetic patient. The treatment varies depending on the factors such as nature of the stress and Prakriti of the individuals.

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Conflicts of interest

There are no conflicts of interest.

References

1. Ranbir S, Reetu K. Stress and hormones. Indian J Endocrinol Metab 2011;15:18-22.
2. Mangione-Garves CA, Kravitz L. Cortisol Connection: Tips on Managing Stress and Weight. Available from: https://www.unm.edu/~kravitz/Article%20folder/stresscortisol.html. [Last accessed on 2017 May 21].
3. Chadha P. Stressors-External and Internal. Available from: http://ezinearticles.com/?Stressors—External-And-Internal&id=134317. [Last accessed on 2017 May 21].
4. Carter WR, Herman J, Stokes K, Cox DJ. Promotion of diabetes onset by stress in BB rat. Diabetologia. In: Weiner IB, Nezu AM, Nezu CM, Geller PA, editors. Handbook of Psychology. Vol. 9. Wiley Online Publication; 1987. p. 674-5. Available from: https://books.google.co.in/books. [Last accessed on 2018 Mar 12].
5. Available from: https://helpguide.org/articles/stress/stress-symptoms-causes-and-effects.htm. [Last accessed as well 2017 May 21].
6. Vaidya SH, editor. Astanga Hridayam of Vagabhatta, Sarera Sthana. Ch. 3, Ver. 83. Reprint edition. Varanasi: Choukambha Vishwabharati; 1996. p. 236.
7. Acharya YT, editor. Caraka Samhitha of Agnivesha. Vimana Sthana. Ch. 8, Ver. 97. Reprint edition Varanasi: ChoukambhaKrishnadas Academy; 2010. p. 277.
8. Bener A, Abdulla OA, Al-Hamaq, DafeeEH. High prevalence of depression, anxiety and stress symptoms among diabetes mellitus patients. Open Psychiatry J 2011;5:5-12. Available from: https://pdfs.semanticscholar.org/108a. [Last accessed on 2017 May 23].
9. Vaidya BH, editor. Astanga Hridayam of Vagabhatta. Chikitsa Sthana. Vol. 19, Ch. 7, Ver. 10. 9th ed. Varanasi: Choukambha Orientalia; 2005. p. 711.
10. Available from: http://isma.org.uk/wp-content/uploads/2013/08/ Stress-Questionnaire.pdf. [Last accessed on 2017 May 23].
11. Surwit RS, van Tilburg MA, Zucker N, McCaskill CC, Parekh P, Feinglos MN, et al. Stress management improves long-term glycemic control in type 2 diabetes. Diabetes Care 2002;25:30-4.
12. Pace TW, Hu F, Miller AH. Cytokine-effects on glucocorticoid receptor function: Relevance to glucocorticoid resistance and the pathophysiology and treatment of major depression. Brain Behav Immun 2007;21:9-19.
13. Bellush LL, Rowland NE. Stress and behavior in streptozotocin diabetic rats: Biochemical correlates of passive avoidance learning. Behav Neurosci 1989;103:144-50.
14. Surwit RS, Schneider MS, Feinglos MN. Stress, hyperglycemia, and ketosis. Diabet Care 1992;15:137-46. Available from: https://pdfs.semanticscholar.org/.../c63cb0a11e7db5ca716b61. [Last accessed on 2018 Mar 14].
15. Sundram BM, Dahlui M, Chinna K. Effectiveness of progressive muscle relaxation therapy as a worksite health promotion program in the automobile assembly line. Ind Health 2016;54:204-14.
16. Vaidya HN, editor. Astanga Hridayam of Vagabhatta, Sarira Sthana. Ch. 3, Ver. 90-95. Reprint edition. Varanasi: Choukambha Vishwabharati; 1996. p. 237.
17. Vaidya HN, editor. Astanga Hridayam of Vagabhatta, Sutra Sthana. Ch. 12, Ver. 13. Reprint edition. Varanasi: Choukambha Vishwabharati; 1996. p. 91.
18. Acharya YT, editor. Charaka Samhita of Agnivesha. Nidana Sthana. Ch. 4, Ver. 24. Reprint edition. Varanasi: Chowkhambha Prakashan; 2013. p. 214.

19. Available from: http://isma.org.uk/wp-content/uploads/2013/08/Stress-Questionnaire.pdf. [Last accessed on 2017 May 23].

20. Ramakrishnan PK, Surendran E, et al. [Dissertation Work] Study on Anger (Krodha) with Special Reference to Paithika Unmada and its management with Mahatikthakagritha. Kottakkal: University of Calicut; 2008.

21. Acharya YT, editor. Charaka Samhita of Agnivesha. CikitsaSthana. Ch. 6, Ver. 18. Reprint edition. Varanasi: Chowkhambha Prakashan; 2013. p. 446.