



## MADHUMEHA: HOW MUCH OF AN AUTOIMMUNE DISEASE?

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### ABSTRACT:

Acharya Charaka has explained *Madhumeha* as a clinical condition characterized by *Prabhoota avila mutrata* in which patient voids the urine which is similar to *Madhu* i.e., having *Kashaya* and *Madhura rasa*, *Pandu varna* and has *Ruksha guna*. In modern parlance, Diabetes mellitus is correlated and understood under the umbrella of *Prameha*. Autoimmunity refers to immune system over activity. Most commonly type 1 Diabetes mellitus is said to be caused due to autoimmunity. Many research works are being done to rule out the influence of autoimmunity in type 2 diabetes mellitus. In Ayurveda also it is important to understand the presence of auto immunity in *Madhumeha* and differentiation in terms of *samprapti* has to be analysed to find out the root cause and involvement of auto-immune pathology in different types of *Madhumeha*. In *Prameha vyadhi* auto immunity can be understood based on the *nidana* and involvement of *dosha-dushya* which decides the prognosis. Autoimmune pathology is seen commonly in *sahaja Prameha* and to some extent can be understood in *apthyanimittaja meha* which has the dominance of *ama* and *pitta* dosha causing inflammatory changes. In this article an attempt is made to compile and analyse the data about the concept of autoimmunity in the *samprapti* of *prameha* which helps in assessing the prognosis and thereby helps in planning the treatment accordingly.

**Keywords:** *Madhumeha*, type 2 diabetes mellitus, Autoimmune disease, *Prameha*

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## INTRODUCTION

According to Ayurveda *basti ashrita rogas* are of two types. One is *mutra atipravrittaja* like 20 types of *Prameha* and *mutra apravrittaja* like *mutraghata*, *mutrakrichra* and *mutra ashmari*. *Prameha* is considered as one among the *maha rogas* as *basti* is involved. According to *Roga namakarana siddhanta*, a disease is named based on *ruja*, *varna*, *samutthana*, *sthana* and *samsthana*. *Samsthana* is *lakshana* and as *mutra atipravrutti* or *prabhuta mutrata* is a *lakshana* it is named as *Prameha*. *Basti* is a *marma* and diseases involving this in general is difficult to cure. *Madhumeha* is one among the 20 types of *Prameha* which can manifest either due to *sahaja karana* or *vatoibana* as seen in hereditary pathology or that which is caused due to *avarana* or *Apathyanimittaja karana* that is seen in acquired pathology.

*Prameha* is commonly correlated with Diabetes mellitus as they share the common clinical features. In the term Diabetes, Dia in Greek means excessive passing, Betise in French is untimely and Mellitus is sweetness of urine. Diabetes mellitus can be caused due to endocrine, metabolic or due to autoimmune pathology.

Autoimmunity refers to immune system over activity. Most commonly type1 Diabetes mellitus is said to be caused due to autoimmunity. Some research works are showing the influence of autoimmunity in type 2 diabetes mellitus also.

To date, there are no preventive or immunosuppressive therapies that can prevent

damage or disease manifestations. However, our increasing knowledge of pathophysiology and immunogenetics has important therapeutic implications for measures aimed at prevention. New approaches for immune therapy such as anti-CD3 antibodies have shown success in modulating the natural history of the disease without the need for chronic immunosuppression. In the near future, it is likely that combination approaches will be needed to bring about lasting remission of the disease<sup>[1]</sup>.

In Ayurveda the concept of autoimmunity is understood in terms of *ama* and *vyadhi kshamatva vaiparitya*. Presence of auto immunity in *Madhumeha* has to be assessed and differentiation in terms of *samprapti* has to be analysed to find out the root cause and involvement of auto immune pathology in different types of *Madhumeha*. This would help us to plan the *chikitsa* accordingly and gives more scope for administering *rasayana chikitsa* in *madhumeha* for bringing about immuno modulatory effect by using ayurvedic medicines for effective management.

## METHODOLOGY

Ayurvedic literatures, modern texts and online search of PubMed, Scope med, Cochrane library, Dhara online and other allied databases were done and reviewed regarding *prameha nidana*, *samprapti*, *chikitsa*, concepts regarding *ama*, *vyadhikshamatwa*, *ojus*, *bala*, *viruddha ahara*, autoimmunity and Diabetes mellitus. The search criteria were to identify potentially relevant

articles and data reporting prevalence of association between auto-immune disease and *Prameha*.

### **Autoimmune diseases in Ayurveda**

According to Ayurveda, the autoimmune disorders can be understood to be caused due to two possible pathologies:

- 1) *Ama* due to *agni vaishamyata*
- 2) Impairment in *vyadhikshamatva, bala* and *ojoyapat*.

As the exact causative factors for auto-immune diseases in terms of *nidana* cannot be elicited, one can understand the possible *samprapti* by the presentation of the disease in different auto-immune diseases.

Auto-immune disease is a resultant of malfunctioning of immune system. This is usually caused due to inflammatory pathologies which trigger the immune system. Inflammation is caused by lack of cellular recognition or communication and the breakdown in this communication is due to cells being covered with *Ama* and this *ama* is caused by *mandagni*.

Thus, the root causes of auto-immune disorders are low *Agni* and weak *ojus* and hence ayurveda treatment focuses on restoring *Agni* and *Ojus*. By strengthening *Agni* and *Ojus*, one can naturally reverse the disease process and restore balance to the system.

### **Autoimmune Pathogenesis in Diabetes**

Autoimmune process does the slow destruction of a particular cells or tissue or can stimulate excessive growth of an organ or interfere in its function. This can be organ specific or non-organ

specific. If this pathology is affecting pancreas it can lead to Autoimmune Diabetes Mellitus.

### **Autoimmune aspects of type 1 Diabetes mellitus:**

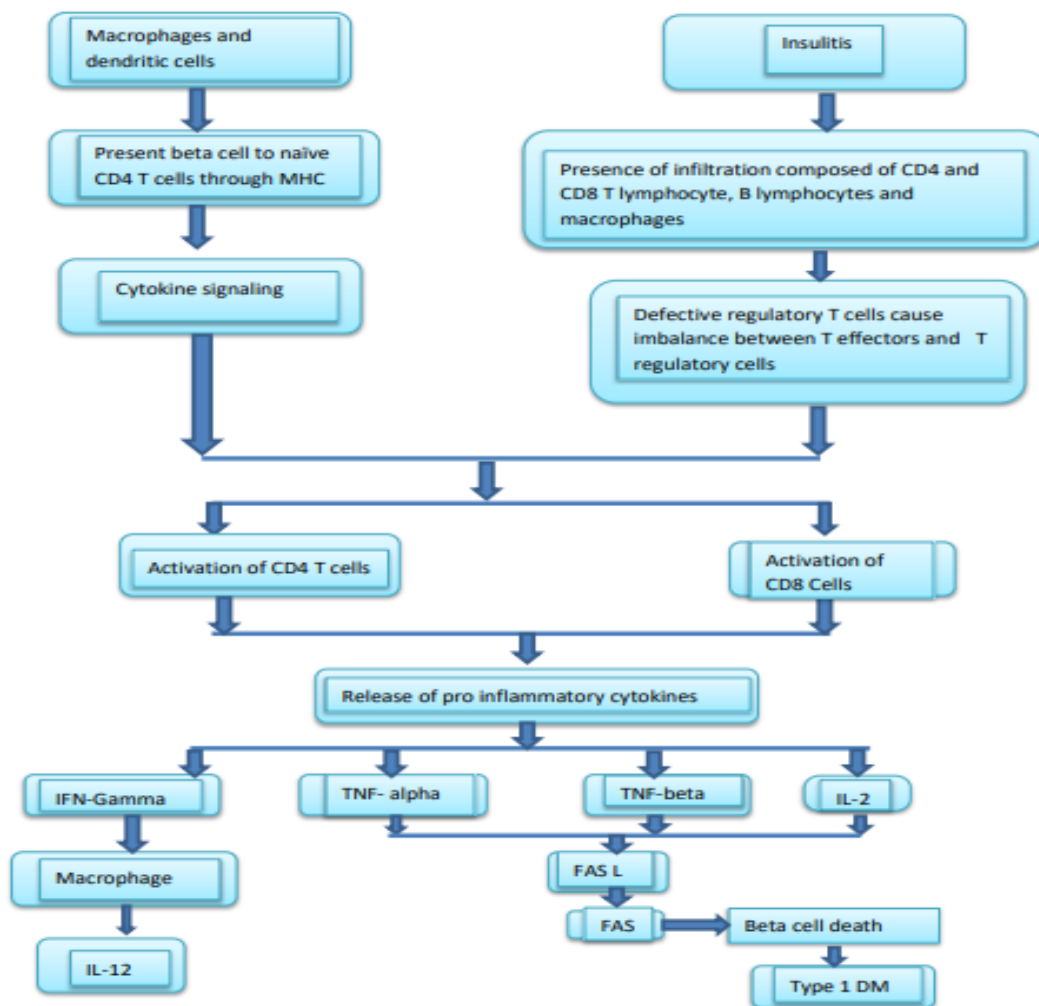
Type1 Diabetes mellitus is commonly considered as Autoimmune diabetes mellitus which is an organ-specific autoimmune disease that affects the insulin-producing pancreatic beta cells, after an inflammatory process leading to a chronic deficiency of insulin in genetically susceptible individuals<sup>[2]</sup>. Genetic predisposition and environmental factors are implicated in the pathogenesis of Diabetes mellitus. The pattern of inheritance and interactions between genetic and environmental factors differ in both type 1 and type 2. Type 1 DM is not genetically determined but increased susceptibility to the disease may be inherited. About 95% of patients with T1DM have HLA-DR<sub>3</sub> or HLA-DR<sub>4</sub> genes which are markers of susceptibility<sup>[3]</sup>. Several features suggest that T1DM has a significant environmental component. An infectious agent such as a virus in the general population is increasing and causing infectious processes<sup>[4]</sup>. The most common appearance of the disease in winter months and some epidemic flares of T1DM suggest that certain viruses such as rotavirus<sup>[5]</sup> and Coxsackie virus <sup>[6]</sup> and some dietetic aspects may influence the risk of developing T1DM. Some studies provided evidence that early (<3 months) introduction of cereals may increase the development of islet autoimmunity<sup>[7]</sup>. Vitamin D and ω-3 fatty acids, which can influence the immune function and

toxins derived from Streptomyces bacteria found in soil, which can colonize foods like vegetables have also been associated with the risk of diabetes<sup>[8]</sup>.

Another scenario, called “hygiene hypothesis” suggests that environmental factors may inhibit the development of autoimmunity. The environment for children is cleaner today, which may lead to defective immuno-regulatory mechanisms that result in a Th2 mediated-response pattern such as asthma or diseases characterized by a Th1 pattern such as T1DM<sup>[9][10]</sup> Over 90% of the patients with new onset

T1DM possess at least one autoantibody against components of the pancreatic islets. They include insulin, the isoform of glutamic acid decarboxylase 65 and 67 (GAD 65 and GAD 67 respectively) and the IA-2 secretory protein, which has a domain like-tyrosine phosphatase. These autoantibodies are markers of the autoimmune process rather than the direct effectors of damage<sup>[11]</sup>. The presence of autoantibodies in relatives of patients with T1DM or in healthy individuals has a significant positive predictive value for disease development.

**Pathogenesis:**



**Fig.1 : Pathogenesis of Type 1 DM**

### **Autoimmune aspects of type2 diabetes mellitus:**

Indicators of autoimmune involvement include the persistent presence of circulating autoantibodies or self-reactive T cells which affect target organs, evidence of lymphocytic infiltrates in target organs, tissue damage, association with other autoimmune disease, and evidence of beneficial effects from immunosuppressive therapy. Manifestations of autoimmunity are detectable in numerous pathologic conditions, which do not fall under the category of autoimmune diseases. Type 2 diabetes is one such example<sup>[12]</sup>.

A hallmark of autoimmune involvement in T2DM is the presence of circulating autoantibodies. Consistent evidence of islet cell autoimmunity in T2DM patients was reported in 1997 by Turner et al.,<sup>[13]</sup> with the identification of glutamic acid decarboxylase (GAD) and islet cytoplasm autoantibodies in 12% of over 3,000 T2DM patients aged between 25 and 65 years<sup>[14]</sup>. In phenotypic T2DM patients older than 65 years, anti-GAD and/or anti-insulinoma-associated protein 2 (IA-2) autoantibodies have been detected in 12% of patients and the existence of subsets of patients with T2DM phenotype and islet cell autoantibodies has been shown by several studies<sup>[15]</sup>.

Multiple factors are involved in its pathogenesis, from genetics to environment.

Diabetes development based on combined cellular autoimmunity and insulin resistance has been reflected by various terms, such as double diabetes, latent autoimmune diabetes of the adult (LADA) or the young (LADY) or type 1.5 diabetes mellitus.

Anti-inflammatory and immunomodulatory therapies have proven effective in improving the metabolic profile of many T2DM patients, possibly by interfering with autoimmune processes and thereby halting the decline of  $\beta$ -cell function.

Obesity is by far the main underlying factor causing T2DM and its pathological potential lies in obesity-associated insulin resistance, activation of innate immunity and chronic low-grade inflammation<sup>[16]</sup>.

As plenty of pathological alterations characteristic of this disease –such as obesity-associated chronic adipose tissue inflammation and  $\beta$ -cell stress induced by gluco- and lipotoxicity – continuously provide danger signals which cause an activation of both innate and adaptive immunity. Danger signals include any molecules resulting from cellular distress which binds to pattern recognition receptors, such as toll-like receptors (TLRs) and nucleotide-binding oligomerization domain (NOD) receptors and cause a local or generalized immune response<sup>[17]</sup>. This response consists in the assembly of a cytosolic protein complex

composed of nucleotide-binding and leucine-rich repeat containing proteins (NLRs) and

caspase 1 which, once activated, triggers IL-1 $\beta$  production.<sup>[18]</sup>

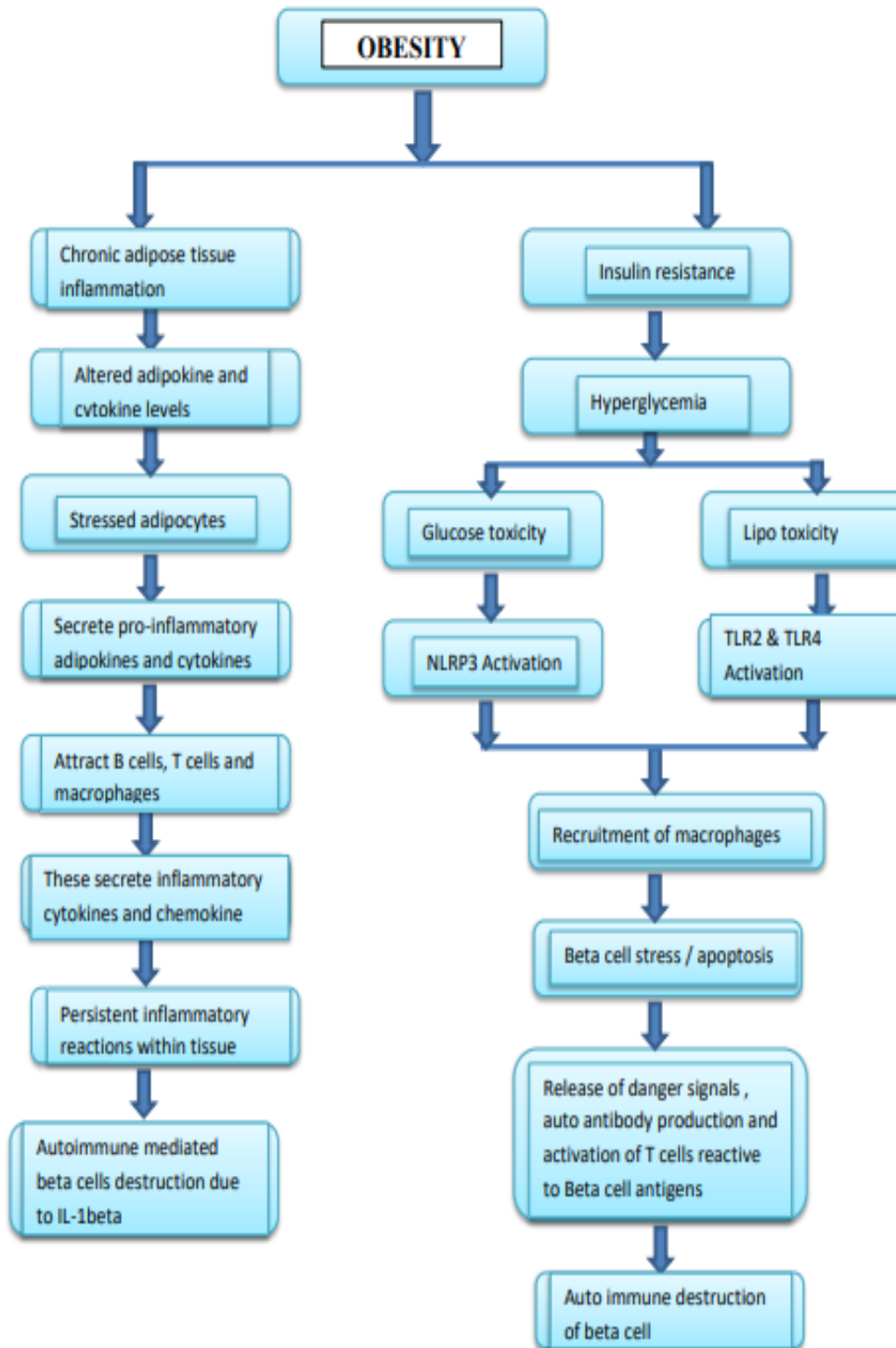


Fig.2 : Autoimmune pathogenesis in DM

**Understanding Autoimmune pathogenesis in Madhumeha**

Acharya Charaka has explained *Madhumeha* as a clinical condition characterized by *Prabhoota avila mutrata* in which patient

voids the urine which is similar to *Madhu* i.e., having *Kashaya* and *Madhura rasa*, *Pandu varna* and has *Ruksha guna*<sup>[19]</sup>.

In *Prameha vyadhi* auto immunity can be understood based on the *nidana* and involvement of *dosha-dushya* which decides the prognosis. Autoimmune pathology is seen commonly in *sahaja Prameha* and to some extent can be understood in other *meha* also due to presence of *ama* and *pitta dosha* in the *samprapti* causing inflammatory changes. Acharya Sushruta has highlighted the presence of *ama* in the *samprapti* of *Prameha*. *Nidanas* like *divaswapna*, *avyayama*, *alasya prasakta*, indulgence in consuming *sheeta*, *snigdha*, *Madhura*, *medhya* and *drava annapana* aggravates *tridosha* resulting in the formation of *aparipakva* dhatus like *medas*, *vasa* etc., which further proceeds to manifesting *Prameha*<sup>[20]</sup>.

In Ayurveda, *ama* is the real cause of varieties of autoimmune disorders which is outcome of faulty *Agni*. One of the features of *Ama* is that once it enters the cycle of *dhatu* formation, it impairs the nutrition and functioning of the *dhatu*s. *Ama* takes *ashraya* in *sthana* where there is *khavaigunyata*. The formation of *Ama* at Gastro intestinal tract level and its intensity and virulence depend upon the status of *Kayagni*, further it changes the integrity of Gastrointestinal mucosa and absorbs and goes into systemic circulations and gets localized in

the cells or organs and induces disorders in due course of time<sup>[21]</sup>. The ancient concepts of *Ama* and its role in the genesis of disease is quite similar to the Leaky gut syndrome of modern medicine which is responsible for variety of autoimmune disorders of unknown etiology<sup>[22]</sup>. *Doshas* gets vitiated in a specific manner, first *Kapha* with an increase in congestion followed by *Pitta* which sets up a cycle of inflammation and then *Vata* which is responsible for degenerative changes or *kshaya*. *Dhatu kshaya* is responsible for further aggravation of *vata dosha* and results in incurable *vataja Prameha*. Acharya Bhavaprakasha has explained that *Prameha* can manifest as an *upadrava* due to *jwara*. Patients suffering from *jwara* are advised not to move even for *mala mutra visarjana* and should be fed in the place where they sleep. This indicates the inflammatory changes due to increased *pitta* causing pancreatitis resulting in destruction of  $\beta$ -cells resulting in Diabetes mellitus. Another important aspect to be understood with respect to autoimmunity in ayurveda is that an autoimmune disease is a resultant of malfunctioning of immune system. The immune system is a network of organs, cells and molecules that work together to defend the body against attacks by foreign invaders such as germs, bacteria, viruses, parasites and fungi. The body's first line of defence is the

skin and mucous membranes is the house of macrophages and antibodies. The macrophages job is to digest the antigens while the antibodies trap the antigens that got away. If the antigens break through these barriers, the body reacts by producing lymphocytes programmed to attack and kill the antigen. In general terms, when antibodies are directed against the body's own cells or when B and T cells attack and destroy their own body's cells and not foreign antigens, an auto immune disorder can result. In Diabetes mellitus, immune system over activity results in degeneration of pancreatic  $\beta$ -cells due to inflammatory pathologies which trigger the immune system. Inflammation is caused by lack of cellular recognition or communication. The breakdown in communication is due to cells being covered with ama and this results in impaired perception and feedback mechanism which is maintained by endocrine system. Neuro-endocrine-immune axis is said to be influenced by exercise, circadian rhythms, seasonal variations, different psychological states etc., Ayurvedic principles of *Vyadhi-ksamatva*, *Ojus* and *Bala* has to be considered to understand the influence of *Vyadhi-ksamatwa* in autoimmune pathology. Chakrapanidatta has interpreted the term *Vyadhi-kshamatwa* as *Vyadhi bala Virodhitwa* i.e., antagonistic to the strength and virulence of the disease and *Vyadhyutpada*

*Pratibandhakatwa* <sup>[23]</sup> i.e., the capacity to inhibit and bind the causes and factors of the disease. Impairment in this *Vyadhikshamatva* can lead to hyperactivity of the immune system.

Charaka has described in *Jwara chikitsa adhyaya*, *Aarogya* is termed as *adhishtana* of *bala* which means *Arogya* or health in general is dependent on *Bala*<sup>[24]</sup>.

The concept of immunity is directly related to combating the diseases and preventing its occurrence, which in ayurveda can be considered as *Bala* which influences physiology of health and pathology of diseases. *Prakruta kapha* contributes to *sharira bala* and is called as *Ojus* which is the *saara* of all the *dhatu*<sup>[25]</sup>. The words *Bala* and *Ojus* have underlying meaning of biostrength and vitality with natural resistance against ageing and disease. *Ojus* has the property like *Prakruta Slesma* <sup>[26]</sup> and is also considered as *Rasa* <sup>[27]</sup> and *Rakta* <sup>[28]</sup>. *Ojus* is important and significant in the context of *Vyadhiksamatwa*. The two kinds of *Ojus* have direct influence on the body's defense mechanism. They combat decay, degeneration, infections and resists such factors which are produced during the vital activities of the organism which may lead to *dhatu hrasa*. If the functioning of *Ojus* is impaired it can lead to various diseases like *Prameha*, *Rajayakshma*, *Pandu*, *Arbuda*, *akalaja jara*, *dhatu khsaya* etc., The action of *Ojas*

relating to *prakruta shleshma* and its presence in all the *dhatu*s confers adequate protection to the *Dhatu*s against decay and degeneration and provides the body with an appropriate substance, which inhibits, neutralizes and destroys the virulent factors causing diseases. These are related to the immunological factors both cellular and humoral, which destroy or neutralizes the disease-causing agents which invade the body. The recent understanding of neuro-endocrine-immune axis in relation to the influence of exercise, circadian rhythms, seasonal variations, different psychological states on immune system has been dealt in Ayurveda long ago. In *Charaka Samhita*, *sutra sthana* it is told that *shareera upachaya, bala, varna, sukha* in terms of health and life span is dependent on three factors namely *anupahata dhatvagni, vayu* and *srotas*. The food we ingest gets transformed into different *dhatu*s and imparts good health only when the above said factors functions properly<sup>[29]</sup>. The food taken by a person decides the state of health or ill health and the state of immunity with the influence of *agni, vayu* and *srotas* which can be understood with that of neuro-endocrine-immune axis. Unfolding many such issues brings the modern concept of immunity closer to Ayurvedic principles of *Vyadhi-kshamatva, Ojus* and *Bala*. Any impairment in *Vyadhi-kshamatva, Ojus* and *Bala* leads to disorders

related to immune system like Auto immune disorders.

## DISCUSSION

Autoimmunity is a highly complex, multifactorial process defined by loss of self-tolerance and chronic excess reactivity of B and T cells stemming danger signals released when cells or tissues undergo abnormal cell death. In ayurveda, the root cause for autoimmune disorders is understood as *mandagni* which further causes *anyonya murchana* of *doshas* and *dooshana* of *dushya* resulting in *dosha dushya sammurchana* followed by manifestation of *vyadhi*. Autoimmune disorders manifest in different parts of the body and at first glance, appear to be unrelated. But the common factor underlying all Auto-immune disorders is inflammation. With our basic understanding of the *dosha*, we see *pitta* predominant constitution are more prone for these diseases. Not only *pitta* even *vata* and *kapha dosha* are equally involved in the pathogenesis of Autoimmune disorders. When *vata* dosha increases in the presence of high *pitta* it is like wind blowing on a fire. This inflammation spreads very rapidly causing organ damage. Acharya Vagbhata has clearly stated that *upahata agni* is the primary stage in the pathogenesis of *Prameha*. As mentioned by Acharya Sushruta, *ama* formed in the *samprapti* of *meha* causes *tridosha* vitiation resulting in the manifestation of *aparipakva*

*dhatu*. This leads to the inflammatory changes in pancreas leading to  $\beta$ -cell dysfunction and impaired insulin secretion causing hyperglycemia. This is also evident in Bhavaprakasha where it is mentioned that *Prameha* can manifest due to *jwara*. Ayurveda treatment for *Meha* focus on restoring *Jatharagni*. In *abhishyanna deha* due to excess accumulation of water, *agni upahata* happens. Owing to this, all the *ahara* taken by the person gets converted into *mutra* and *medas* only. Hence treatment should aim at enhancing the *tejo dhatu* and pacifying *kleda* and *medas*. This impairment in the *agni* can also cause *vaiparitya* of *vyadhikshamatva*, *bala* and *ojus*. As autoimmune disorders are due to malfunctioning of immune system, one must concentrate on improving this defence mechanism in the diabetic patients. In both type 1 and type 2 Diabetes mellitus studies are showing the involvement of auto immunity. Along with Anti diabetic treatment, immunomodulation therapies are advised for better response. In Ayurveda this concept has been mentioned before ages and has given much importance to *Rasayana chikitsa* along with *shodhana* and *shamana chikitsa* in the management of *Prameha*. In ayurveda, at most importance is given for preventing the diseases along with different treatment protocols explained for the manifested ones. It is very clearly stated by Acharya Charaka

that person who do not follow *swasthavrutta* prescribed for maintaining positive health suffers from diseases due to *dosha vaishamyata*, and hence those who are desirous to remain *swastha* or disease free should follow all the regimen conducive for health. To prevent the *nija vyadhi*, it is very much important to administer *rutu prakara shodhana* followed by intake of suitable *Rasayana* and *vrushya yoga* to maintain homeostasis of dhatus and slow the process of senility.

## CONCLUSION

As mentioned by Acharya Charaka, it is always wise to properly assess and analyse the *samprapti* before starting the treatment. As mentioned in Charaka Samhita, after ascertaining the diseases based on *lakshana* one should analyse the *dosha* and *dushya* involved in *samprapti* and further treat the *sadhya vyadhi* with *viparita* or *viparitartakari chikitsa* which pacifies the *dosha* and the *vyadhi*, with due considerations to *matra* and *kala*. In *Prameha vyadhi*, if there is involvement of autoimmune pathology it cannot be managed only by adopting *pramehahara chikitsa*. Understanding the autoimmunity in *Prameha* helps us to gain the wider knowledge of the pathogenesis in the disease which can be reflected in the newer concepts of its treatment involving *Rasayana chikitsa* for immunomodulatory action in the

management of *Prameha*. Inflammatory response occurs as a result of the immune response to high blood glucose levels as well as the presence of inflammatory mediators produced by adipocytes and macrophages in fat tissue. This low and chronic inflammation damages the pancreatic  $\beta$ -cells and leads to insufficient insulin production which results in hyperglycemia. This immune system dysfunction makes diabetic people more susceptible to infections, acute sickness, and chronic illness. Hence a better understanding of how immune dysfunctions are involved in the pathogenesis of *Prameha* can lead to probing of novel treatments and prevention of infectious diseases and comorbidities, thus improving the outcome of treatment in type 2 Diabetes mellitus patients. The role of immunomodulation therapy with ayurvedic interventions in the form of administering *Rasayana dravyas* like *Guduchi*, *Haridra*, *Shilajatu*, *Trivanga*, *Shatavari*, *Brahmi* etc., to preserve the residual insulin secretion by checking the inflammatory process, thereby preserving beta cell function has to be further studied and analysed.

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