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UNDERSTANDING AVARANA IN RELATION WITH INSULIN RESISTANCE W.S.R TO MADHUMEHA

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ABSTRACT
Madhumeha is a disease known to mankind since time immemorial. It is a type of Vataja Pramaeha, among the twenty varieties of Prameha explained in our classics. Madhumeha is characterised by mutra and tanu madhuryata and similar clinical features are observed in Diabetes mellitus. Two types of pathologies can occur in Madhumeha. In first type Vata prakopa is due to Dhatu kshaya which is said to be asadhya and second type where Madhumeha occurs due to Avarana to gati of Vata by vriddhi of Kapha, Pitta, mamsa or medas individually or in combination. This pathology can be understood with respect to Insulin resistance seen in type 2 Diabetes mellitus, which can be corelated with various conditions like Inflammatory changes, Glucose toxicity, amyloid deposition and Lipid toxicity in relation with Insulin resistance. Analysing the avaraka will help in proper understanding of samprapti which further help in planning up the accurate treatment. Hence an attempt is made in this paper to understand avarana in relation to Insulin resistance caused by Kapha dosha as the Glucose toxicity, Pitta dosha in the form of Cytokines synthesis causing inflammation, Mamsa avarana causing amyloid deposition and medo avarana by lipid toxicity.

KEYWORDS: Prameha, Madhumeha, Avarana, Type 2 Diabetes mellitus, Glucose toxicity, Lipid toxicity, Insulin resistance.

INTRODUCTION

Prameha is a mootra ati pravrittaja roga which affects basti marma and is characterised by prabhoota mutrata and avila mutrata.[1] Prameha is further classified into 20 varieties based on physical abnormalities of urine. Prameha is a complex syndrome encompassing Obesity, Metabolic syndrome and Diabetes Mellitus. However, all pramehas if neglected may lead to Madhumeha, a type of Vataja prameha presenting with mutra and tanu madhuryata.[2] Thus, Madhumeha can be considered as an advanced stage of Prameha. Acharya Charaka and Acharya Sushruta have described two types of Prameha based on the onset as Jatataha / Sahaja Pramehi and Sthula / Apathyanimittaja Pramehi which find similar connotations in contemporary science.

The disease Diabetes Mellitus which is presenting with excessive urination with sweet smell and taste like honey reflects the Ayurvedic term Madhumeha. Diabetes Mellitus is a heterogeneous group of disorders characterized by variable degrees of insulin resistance, impaired insulin secretion, and increased hepatic glucose production.[3]

Acharya Charaka has explained about etiological factors and pathogenesis of avarana janya Madhumeha in sutra sthana. Avarana here can be understood as the Insulin resistance and this avarana can be caused by Pitta, Kapha, Mamsa or Medas which can be corelated with various conditions like Inflammatory changes, Glucose toxicity, amyloid deposition and Lipid toxicity in relation with Insulin resistance. Analysing the avaraka will help in proper understanding of samprapti which further help in planning up the accurate treatment.

Homeostasis in the Body

The homeostasis in the human body is maintained by extraordinary number of systems to maintain stable blood glucose and to avoid broad swings in its level. These systems include hormones that are directly or indirectly generated by the diet. These hormones sense dietary nutrients and send appropriate neural signals to the brain specifically the hypothalamus to orchestrate fuel usage for either oxidation into energy or long-term

storage. The central hormone involved in this metabolic communication system is insulin. However, increased inflammation can disturb these complex communication systems eventually leading to metabolic defects such as obesity, metabolic syndrome, and diabetes.[4]

In Ayurveda the similar concept has been explained years ago. Acharya Charaka has explained that Ahara taken by a person only can impart good health provided three important factors namely Sarva dhatvagni (tissue specific digestion and metabolism), Srotas (Channels of circulation) and Vayu are unaffected or unimpaired.[5]

Further understanding of the three factors of upahata and anupahata states of Srotas, Maruta and Sarva dhatu ushma helps in analysing the swastha or rogaavastha and deducing samprapti in Vyadhi avastha.

1. Anupahata maruta is responsible for the neuro-endocrine functions happening in the body. When Vata dosha is in equilibrium state there will be no hinderances to the functioning of neural system and endocrine system by which there will be proper secretion of hormones, proper utilization of the hormones by the target cells and proper functioning of the hormones by which the ahara taken will be properly metabolised and impart good health.
2. Anupahata srotas is the srotas which circulates vata which can be considered as the nervous system. If there is any damage to the nervous system by which neuro transmitters does not pass the nerve impulses properly to any part of the body, it results in impaired functioning in the target organ by which the hormones cannot be utilized properly. In other instances, if there is any upaliptata in the srotas due to increased consumption of guru, snigdha or madhura aharasevana, which causes increase of kapha dosha leading to lepana or upaliptata of srotas. Due to this upaliptata there is resistance offered to the action of Insulin like hormones by which the physiological functions of Insulin are hampered. Though there is normal secretion of the Insulin due to the resistance offered by the cells, there is hyperglycaemia in the blood.
3. Anupahata Dhatu ushma is the tissue specific digestion and metabolism. Different types of ahara ingested stimulate antargni and get properly digested by respective bhutagni. Further in due course of time food gets transformed into dhatus in the presence of dhatvagni by the process of dhatvagnipaka. If there is upahata dhatu ushma which leads to improper metabolism by which hormones are not secreted properly such as hyposecretion of the Insulin from Pancreas.

The Hypothalamic Pituitary Adrenal (HPA) axis is our central stress response system. The HPA axis is an eloquent and dynamic intertwining of the CNS and Endocrine system. When there is impaired co-ordinated action of nervous system and endocrine system which maintain the stable blood glucose due to upahata maruta, upahata srotas and upahata dhatu ushma, it presents with the samprapti of avara janya Madhumeha. Type 2 diabetes is due to the combination of insulin resistance and β-cell failure, the latter preventing sufficient insulin secretion to overcome the insulin resistance.

Arambhaka Dosha Causing Insulin Resistance

The association of obesity with type 2 diabetes has been recognized for decades, and the major basis for this link is the ability of obesity to engender insulin resistance. Insulin resistance is a fundamental aspect of the etiology of type 2 diabetes and is also linked to a wide array of other pathophysiologic sequelae including hypertension, hyperlipidemia, atherosclerosis i.e., the metabolic syndrome, or syndrome X, and polycystic ovarian disease. Although many details of the mechanisms by which the enlarged adipose tissue mass that defines obesity causes systemic insulin resistance remain unknown, the past several years have witnessed an explosive increase in our understanding of what may now be referred to as the adipo-insulin axis. There are also grounds for considering the related possibility that insulin resistance and hyperinsulinemia, in addition to being caused by obesity, can contribute to the development of obesity.

The ahara rasa is the prime factor which results in sthoulya or karshya. Acharya Sushruta while explaining about the samprapti of sthoulya has highlighted that whenever there is exposure to nidanas such as shleshmala aharasevana, adhyashana, avyayama and divaswapna, there will be improper digestion of ahara ingested resulting in Amarasa utpatti. When this ama rasa is accumulated more and attains madhuratara and gets circulated all over the shareera.[6] In this stage when madhuratara ama rasa in the form of Glucose for a longer duration results in hyperglycaemia which we can be considered as the pre-diabetic stage. Further added with ati snigdhamsha results in manifestation of abaddha medas and also the vruddha samleena shlemshma.[7] does upalepana of the srotas resulting in narrowing of lumen and offer resistance to the action of Insulin on a long run causing Insulin Resistance.

According to Acharya charaka when explaining about sthoulya chikitsa has very clearly opined that causative factors such as involvement of shleshma, medas or mamsa has to be assessed first and treatment has to be adopted based on that.[8] This condition has close resemblance with that of Santarpanajanya madhumeha in which the doshas and dushyas are almost similar as sthoulya.

Avarana in avarana janya Madhumeha can be caused due to shleshma, pitta, medas, mamsa individually or in combination. As there is vruddhi of kapha, pitta, mamsa and medas which does avarana to the gati of vayu. This resultant obstruction is very clearly understood by the clinical features of Madhumeha in which functioning of Insulin is impaired due to Insulin resistance.

The avarana in terms of Insulin resistance caused by Kapha dosha, Pitta dosha, Mamsa avarana and Medas avarana can be understood as the Glucose toxicity, Cytokines synthesis causing inflammation, by amyloid deposition and lipid toxicity repectively. Samvibhajya pariksha of avaraka will help in proper planning of treatment by selecting appropriate arishtas for kapha, mamsa and medas as told in sthoulya.

Physiological Role of Insulin

Insulin is a peptide hormone secreted by the β cells of the pancreatic islets of Langerhans and maintains normal blood glucose levels by facilitating cellular glucose uptake, regulating carbohydrate, lipid and protein metabolism and promoting cell division and growth through its mitogenic effects.

Insulin is the pivotal hormone regulating cellular energy supply and macronutrient balance, directing anabolic processes of the fed state. Insulin is essential for the intra-cellular transport of glucose into insulin-dependent tissues such as muscle and adipose tissue. Signalling abundance of exogenous energy, adipose tissue fat breakdown is suppressed and its synthesis promoted. In muscle cells, glucose entry enables glycogen to be synthesised and stored, and for carbohydrates, rather than fatty acids or amino acids to be utilised as the immediately available energy source for muscle contraction. Insulin therefore promotes glycogen and lipid synthesis in muscle cells, while suppressing lipolysis and gluconeogenesis from muscle amino acids. In the presence of an adequate supply of amino acids, insulin is anabolic in muscle.[9]

Mechanisms of Insulin Resistance

Insulin resistance is defined where a normal or elevated insulin level produces an attenuated biological response. Classically this refers to impaired sensitivity to insulin mediated glucose disposal or a condition in which cells are no longer responding appropriately to circulating Insulin. At the cellular level the strength of insulin signalling from its receptor to its final action is reduced in effect. In particular, if insulin receptor substrate-1 (IRS-1) is phosphorylated at a critical serine or threonine positions, this will lead to an accelerated degradation of the phosphorylated IRS-1 protein thereby reducing the strength of insulin signalling.[10]

Compensatory hyper insulinaemia occurs when pancreatic β cell secretion increases to maintain normal blood glucose levels in the setting of peripheral insulin resistance in muscle and adipose tissue.

Physiologically the actions of insulin are influenced by the interplay of other hormones. Insulin, though the dominant hormone driving metabolic processes in the fed state, acts in concert with growth hormone and IGF- 1; growth hormone is secreted in response to insulin, among other stimuli, preventing insulin-induced hypoglycaemia. Other counter-regulatory hormones include glucagon, glucocorticoids and catecholamines. These hormones drive metabolic processes in the fasting state. Glucagon promotes glycogenolysis, gluconeogenesis and ketogenesis. The ratio of insulin to glucagon determines the degree of phosphorylation or dephosphorylation of the relevant enzymes. Catecholamines promote lipolysis and glycogenolysis; glucocorticoids promote muscle catabolism, gluconeogenesis and lipolysis. Excess secretion of these hormones may contribute to insulin resistance in particular settings, but does not account for the vast majority of insulin resistant states. Insulin resistance in most cases is believed to be manifest at the cellular level via post-receptor defects in insulin signalling. Despite promising findings in experimental animals with respect to a range of insulin signalling defects, their relevance to human insulin resistance is presently unclear. Possible mechanisms include down-regulation, deficiencies or genetic polymorphisms of tyrosine phosphorylation of the insulin receptor, IRS proteins or PIP-3 kinase, or may involve abnormalities of GLUT 4 function.[11]

Role of inflammation in Insulin resistance

Insulin resistance can be characterized as a metabolic dysfunction that is often mediated by increased inflammation.

Much of that inflammation may be diet-induced via the role of various dietary fatty acids. In particular, omega-6 and saturated fatty acids (especially arachidonic acid (AA) and palmitic acid) can be viewed as proinflammatory molecules, whereas omega-3 fatty acids (especially eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA)) can be viewed as anti-inflammatory molecules. This is because they have the ability to function as the necessary substrates to generate resolvins as well as binding to specific binding proteins that can decrease insulin resistance in an organ.

Increased cellular inflammation has the ability to interrupt insulin's action by disrupting signalling mechanisms within the cell in particular by the enhancing the phosphorylation of IRS. The primary suspects appear to be inflammatory mediators including the inflammatory cytokine tumor necrosis factor alpha (TNFα) as well as inflammatory protein kinases such as c-JUN N-terminal kinase (JNK) and the IKK complex.

TNFα knock-out animal models are resistant to the development of insulin resistance in animal strains prone to diet-induced obesity (DIO mice) or those that lack leptin (Ob/Ob mice). The JNK pathway is stress-activated and is associated with the presence of M1 activated macrophages. If the IKK complex is activated by inflammation, it phosphorylates IκB (the inhibitor of NF-κB) leading to its rapid degradation. Once IκB is degraded, it can no longer prevent the free entry of NF-κB into the nucleus. Once NF-κB enters the nucleus it causes the expression of additional inflammatory mediators such as cytokines (IL-1, IL-6, TNFα, etc.) and

enzymes such as COX-2. The suggestion that inflammation may be related to insulin resistance came more than a century ago when it was observed that certain anti-inflammatory drugs (salicylates and aspirin) were effective in reducing the hyperglycemia observed in diabetes. It is now known that these drugs are inhibitors of phosphorylation action of the IKK complex.[12]

Glucose toxicity and Insulin resistance

Glucose toxicity means a decrease in insulin secretion and an increase in Insulin resistance due to chronic hyperglycemia. Glucose toxicity indicate a clinical condition where control of diabetes in particular is poor, since hyperglycemia itself reduces the insulin secretion capacity of pancreatic β-cells, and the resultant increase in insulin resistance leads to further hyperglycemia. This vicious circle finally leads to the total incapacity of β-cells to secrete insulin.

Glucotoxicity not only affects the secretion of pancreatic hormones but also participates in insulin resistance of insulin-sensitive tissues, which include liver, skeletal muscle, and adipose tissue. Oxidative stress is also strongly suspected to be involved in chronic hyperglycemia-induced insulin resistance. It has been found that oxidative stress is associated with the molecular mechanism of the decreased insulin biosynthesis and secretion, which is the main etiology of glucose toxicity. Because pancreatic islet cells show extremely weak manifestation of antioxidative enzymes it is thought that the pancreas may be more susceptible to oxidative stress than other tissues and organs. DNA binding capacity of PDX-1 decreases as a result of oxidative stress caused by hyperglycemia, while insulin biosynthesis and secretion also decrease.[13]

Lipid induced Insulin Resistance

Obesity is a well-established risk factor for the development of insulin resistance. Obesity is associated with the increased deposition of lipids in non-adipose tissue with subsequent decreases in insulin sensitivity. Currently, the mechanisms by which increased fat accumulation leads to insulin resistance and metabolic syndrome are not completely understood.

Obesity may set up a state of inflammation in the body leading to increased production of inflammatory cytokines that negatively impact insulin sensitivity. This theory is consistent with studies showing elevated levels of the proinflammatory cytokines IL-6 and TNF-α in individuals with insulin resistance and type 2 diabetes. Alternatively, hormone production by adipose tissue may be dysregulated leading to the increased production of adipokines that cause insulin resistance.

A theory examining the capacity of adipose tissue to store lipids postulates that an individual's capacity to store lipids in adipose tissue has a set maximal limit. When this limit is exceeded, excess lipids spill over into plasma resulting in elevated plasma free fatty acid and triglyceride levels. This results in the increased import and storage of these molecules in non-adipose tissues such as skeletal muscle and liver. The ectopic storage of lipids in non-adipose tissues may result in metabolic derangements via lipid-induced toxicity (lipotoxicity). Lipotoxicity may also contribute to the loss of pancreatic β cells that occurs during the development of type 2 diabetes.[14]

Fat cells do not have an unlimited capacity to expand. Even though the adipose tissue is highly vascularized, the over-expansion of existing fat cells can create hypoxia, which activates the HIF-1 gene. This results in the increased expression of both JNK and IKK thereby creating inflammation within the fat cell. This inflammation, in turn, creates insulin resistance within the fat cell. In the adipose tissue, insulin is normally an anti-lipolytic hormone as it decreases the activity of hormone-sensitive lipase (HSL), which is required to release stored fatty acids. With the development of cellular inflammation and insulin resistance in the fat cell, higher levels of free fatty acids (FFA) can leave the fat cell to enter into the circulation and be taken up by other organs, such as the liver and the skeletal muscles that are unable to safely store large amounts of fat. This leads to developing insulin resistance in these organs. With increased inflammation in the fat cells, there is also a migration of greater numbers of M1 macrophages into the adipose tissue with a corresponding release of inflammatory cytokines, such as TNFα, which further increases insulin resistance and lipolysis.[27]

Obese individuals with insulin resistance have greater levels of both the uptake and release of FFA into and from the adipose tissue. The increase in lipid influx causes an over-load of the synthetic capacity to make triglycerides, and as a result both diacyglycerol(DAG) and ceramide levels begin to increase, which only further increases insulin resistance in the fat cells. If the fat cells cannot expand rapidly enough to store this increasing fatty acid flow, then the excess released fatty acids begin to accumulate in other tissues such as the liver and skeletal muscles, and this begins the process of lipotoxicity that further increases systemic insulin resistance. It is with the development of lipotoxicity that the real metabolic consequences of insulin resistance begin.[15]

The Lipotoxicity hypothesis is supported by studies in which cells are cultured with an excess of long-chain saturated fatty acids complexed to serum albumin. In these studies, apoptosis is induced in a dose dependent manner and is enhanced by high-glucose treatment. Further evidence for the lipotoxicity theory comes from the study of lipid dystrophy patients who have generalized or partial loss of adipose tissue. These individuals with reduced lipid storage capacity often present with severe insulin resistance, dyslipidaemia, and fatty liver.[16]

Role of Amyloid deposition in Insulin resistance

Amyloids are aggregates of proteins characterized by a fibrillar morphology of 7–13 nm in diameter, a β-sheet secondary structure (known as cross-β) and ability to be stained by particular dyes, such as Congo red. In the human body, amyloids have been linked to the development of various diseases. Pathogenic amyloids form when previously healthy proteins lose their normal structure and physiological functions and form fibrous deposits in plaques around cells which can disrupt the healthy function of tissues and organs.

To date, 37 human proteins have been found to form amyloid in pathology and be associated with well-defined diseases. The International Society of Amyloidosis classifies amyloid fibrils and their associated diseases based upon associated proteins and IAPP (Amylin) are said to be associated with Diabetes mellitus type 2, Insulinoma.

The reasons why amyloid cause diseases are unclear. In some cases, the deposits physically disrupt tissue architecture, suggesting disruption of function by some bulk process. An emerging consensus implicates prefibrillar intermediates, rather than mature amyloid fibers, in causing cell death, particularly in neurodegenerative diseases. Studies have shown that amyloid deposition is associated with mitochondrial dysfunction and a resulting generation of reactive oxygen species (ROS), which can initiate a signaling pathway leading to apoptosis.[17]

Insulin resistance is associated with brain amyloid deposition. The body becomes more and more resistant to the blood-sugar lowering effects of insulin as it becomes more overweight. The body recognizes this shift and keeps making more insulin to counter the insulin resistance. Eventually this cycle of insulin resistance and insulin over-production may result in type 2 diabetes. This is significant, as people with diabetes are at a high risk of developing Alzheimer's disease. The researchers used Pittsburgh compound B (PiB), which is a radioactive analog of thioflavin T, to be able to take images of beta-amyloid plaques in the brain using position emission tomography scans. In participants with a normal concentration of sugar in their blood, higher insulin resistance corresponded to higher PiB uptake in frontal and temporal areas. This reflects an increased amyloid deposition in their brain.[18]

DISCUSSION

All prameha are caused by Tridoshas. Madhumeha is a Vata Pradhana Tridoshaja Vikara. Two types of pathologies can occur in Madhumeha. In first type Vata Prakopa is due to Dhatu Kshaya which is said to be asadhya and second type where Madhumeha occurs due to Avarana to gati of Vata by vriddhi of Kapha, Pitta, mamsa or medas individually or in combination. Acharya Charaka in Sootrasthanam, has described Avarana Janya Madhumeha Samprapti and said it is Kricrasadhya. When a person indulges in Prameha nidana in the form of Ahara or Vihara, it leads to increase in Kapha Dosha, Medo Dhatu, Mamsa Dhatu and Pitta Dosha. These Pravridha dosha and dushya does Avarana to the gati of Vyana Vayu and Apana vayu. This Prakupita vayu takes Ojus (blood glucose) to basti where Ojus is expelled out of body through urine is called as Madhumeha. Avarana to the gati of vata dosha or the obstruction in this condition can be understood as the resistance offered to the action of Insulin in different circumstances resulting in increasing blood sugar.

Obesity induces insulin resistance, especially in skeletal muscle or Mamsa dhatu, while weight loss can improve insulin sensitivity in the obese. Increased fat mass decreases whole-body insulin sensitivity which can be understood as the circulating fat derived products in the form of Kapha dosha are presumed to be responsible for causing Insulin resistance. Levels of free fatty acids are raised in obese subjects, apparently because lipolysis is enhanced, and free fatty acids may cause hyperglycaemia by competing with glucose metabolism in liver and muscle. In muscle, free fatty acids inhibit glycolysis at the level of phosphofructokinase and glucose oxidation via pyruvate dehydrogenase, causing a decrease in glucose utilization and a secondary reduction in glucose uptake due to avarana effect.

We can say that high fat derived products hamper the response of target cell like muscle cell insulin receptors to the insulin which we can understand as Avarana by Kapha dosha and Kapha Vargiya dhatu such as medas and mamsa along with Pitta Dosha. This insulin resistance leads to hyperglycemia which leads to renal loss of glucose by urine[19]. This avarana can thus be understood in relation to Insulin resistance caused by Kapha dosha as the Glucose toxicity, Pitta dosha in the form of Cytokines synthesis causing inflammation, Mamsa avarana causing amyloid deposition and medo avarana by lipid toxicity.

CONCLUSION

Type 2 diabetes is due to the combination of insulin resistance and β-cell failure, the latter preventing sufficient insulin secretion to overcome the insulin resistance. As told by Acharya Sushruta all types of pramehas are caused due to the involvement of sarva doshas. Vata, Pitta, Kapha and Medas are involved in the manifestation Kaphaja meha, Vata, Pitta, Kapha and Rakta along with Medas manifests Pittaja meha, Shleshma, Pitta, Vasa, Majja, Medas and Vata are involved in manifesting Vataja meha. By this we can understand that Kapha and Kapha vargeeya dhatus like mamsa and medas along with pitta dosha does avrana to the gati of vata dosha which results in creating resistance to the action of Insulin in the body.

Understanding of the arambhaka dosha causing insulin resistance is important for deducing proper samprapti. In this regard an attempt is been made in this article to

relate the roleof Kapha dosha, Pitta dosha, Mamsa and Medas in terms of Glucose toxicity, increased cellular inflammation, Amyloid deposition and Lipid toxicity in causing avarana or Insulin resistance. This insulin resistance causes hyperglycemia which leads to renal loss of glucose by urine.

Further, this will also help in planning up the appropriate treatment to remove the avaraka and thereby improving the sensitivity of the cells for increasing Glucose uptake and utilization.

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