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A Gender divide in Prameha: Women's Natural Resilience

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ABSTRACT: Prameha is well described in Samhitas with symptoms characterized by profuse urination with several abnormal qualities due doshic imbalance. Acharya Sushruta gave a gender importance that " Streenum Prameha Na Bhavanti, " because " her body undergoes natural shodhana inform of menstruation. Prameha is corelated with Diabetes Mellitus. The data shows prevalence of type 2 DM is worldwide with 17.7 million, more in men than women. Total & diagnosed diabetes prevalence was higher in men (18.0 % & 12.9% respectively) than in women (13.7 % & 9.7% respectively).

KEYWORDS: Prameha, Diabetes Mellitus, Ammenorrhoea, Hyperglycemia

INTRODUCTION

Prameha is combination of two words – 'Pra' upsarga & 'Meha' dhatu. The word Meha is derived from root "Miha Secana"–Sechana means to Moisten. "Pra" suggest excessive. So Prameha is a disease with excessive urination with turbid & sweet quality[1]. Acharya Sushruta in beginning of Chapter of Prameha commented that Prameha does not occur in women, which means Prameha occurs only in men, (Purusha janeeyat Pramehi Bhavishyati)[2]. The reason quoted for non occurrence of Prameha in women is monthly menstrual bleeding, which purifies her body. The doshas responsible for causation of prameha gets flushed out regularly by monthly menstruation,(Rajah prasekanaareenammaasimaasivishodhyet –DalhanaCommentary)[3]. Not only Acharya Sushruta, but in Yogaratnakar, Prameha Cikitsa same concept can be seen. The body gets shodhana effect every month & because of this reason the occurrence of prameha is prevented in women (Na pramehayantahastreeyah)[4]. It conveys the meaning that stoppage or not having regular menstrual bleeding causes Prameha.

According to Ayurveda, menarche or menstruation starts by 12yr & menopause or cessation of menstruation is by 50 yrs[5]. Under normal condition, there is absence of menstruation, is during pregnancy & complete cessation of bleeding after menopause. Both condition have great impact on blood glucose. Many women suffer from diabetes during pregnancy called Gestational Diabetes mellitus (GDM), after delivery the blood glucose come back to normal. The pathophysiology in this condition are hormones made by placenta, which prevents the body from using insulin effectively. Placents produces variety of hormones to maintain pregnancy. Some hormones are Estrogen, Progestrone, Cortisol & Human placenta lactogen which have a blocking effect on insulin called as Contra Insulin Effect. Normally pancreas is able to make additional insulin

to overcome insulin resistance, but production of insulin is not enough to overcome the effect of placental hormones & GDM results.[5]

Many studies shows that after menopause, due to cessation of menstruation, there is increased rate of Diabetes mellitus. As per ayurveda menopause is attained by 50 yrs, but typical age transition can be seen between 45 – 55 yrs.[6] The menopausal transition is characterized by a shift in women's sex hormone profile owing to permanent changes in ovarian function[7]. Menopause, specifically postmenopause, is defined as lack of a spontaneous menstrual period for 12 months[8]. Women have been classified as postmenopausal if they have no menses for several reason (Table 1): naturally, through cessation of ovarian estradiol production or surgically, through removal of their uterus or both of their ovaries. The term "natural menopause" is used to describe cessation of menses for 1 year if women have their uterus & at least part of one ovary. The term "surgical menopause" has been used to refer to women no menses due to surgery & has been used to refer to women who had bilateral oophorectomy, hysterectomy or both[9].

Table 1: Definition of menopause & range of hormone levels in the literature

Term	Definition	Range of E2(pg/ml)	Range of T(ng/dl)	Range of DHEA-S(ng/ml)	Range of SHBG(nmol/l)	Ref
Premenopause	Menses within past 1 year	40-82	18-40	576-1270	43-62	
Natural Menopause	Cessation of menses for 1 year in the presence of uterus & at least part of one ovary.	10-21	24-35	529-708	35-52	
Surgical Menopause						
Hysterectomy	Removal uterus	14	21	474	40	
Bilateral oophorectomy	Removal of both ovaries	3-13	11-17	472-510	43	

Women who have undergone a hysterectomy & retain at least one ovary will have no menses, but these women have hormonal profiles that are similar to the profiles of women who have naturally premenopausal, perimenopausal or postmenopausal. In following paragraph the risk factors, their prevalence during menopause, & studies linking them with increased glucose & diabetes are described.

Androgenicity

The most common active androgens in perimenopausal women include testosterone (T), dehydoepiandrosterone (DHEA)& other androgens such as androstenedione& their metabolites. The fraction of active T may be represented by the free androgen index, which represents the proportion of T not bound to

sex hormone binding globulin (SHBG). SHBG itself is a marker of androgenicity, as SHBG binds more avidly to T than to estradiol (E2), low SHBG levels reflect greater relative androgenicity& high SHBG levels reflect lesser androgenicity.[11] Among women in natural menopause, the hormonal milieu is thought to change in response to the declining pool of ovarian follicles or ovarian reserve. Secretion of inhibin B, a peptide produced by ovarian antral follicles, decreases, and as a result FSH secretion by pituitary gland increases.[12] Initially, E2 levels may actually increase as a result until follicles are depleted to the extent that the ovary no longer produces estrogen.[13] However, in postmenopausal women, the ovaries continue to produce similar level of T & approximately half of the levels of andostenedione compared with premenopausal women.[14] Thus, naturally postmenopausal women have a relatively more androgenic hormone compared with premenopausal women even though their absolute T levels may be slightly lower than premenopausal women. Longitudinal studies of menopausal transition support the concept of increased relative androgenicity due to a decline in estrogen levels. The hormonal milieu probablydiffers between menopause types (Table 1). Among women who had their ovaries removed, overall androgen levels are lower than in women in natural menopause, but these women are still androgenic compared with premenopause, owing to continued androgen production by adrenal glands & lack of estrogen production by ovaries.[15] Among women who retain their ovaries but have undergone hysterectomy, T levels are slightly lower than in natural menopause for unclear reasons, possibly related to unintentional ovarian necrosis during hysterectomy.[15] Hypothetically, menopause could increase glucose levels through greater relative androgenicity. Several types of studies support this supposition. First, greater andogens is associated with higher levels of glucose & insulin in premenopausal women with Polycystic ovarian syndrome.[16] Second, exogenous methyltestosterone leads to increased insulin resistance & increased glucose levelsin clamp studies.[17] Third, epidemiologic studies in premenopausal women & postmenopausal women show associations between SHBG or T with glucose.[18-20]

Adiposity & Insulin resistance

Changes in adiposity may be affected by menopause type. In the SWAN, Sutton-Tyrrell *et al.* found that women undergoing a natural menopausal transition did not have an increased risk of obesity due to menopause *per se*, although their risk increased with age.[10] However, women who had undergone surgical menopause (in this case, meaning hysterectomy and/or oophorectomy) had a significant increase in odds for obesity compared with premenopausal women.[10] Of note, these odds were increased both in women who had and had not undergone oophorectomy.Adiposity may increase risk through several mechanisms, including insulin resistance. Insulin resistance and its associated glucose intolerance are strong predictors of Type 2 diabetes.[21]

Sleep disturbances

Sleep disturbances, that is insomnia or sleep arousal, are common in midlife.[22] In the SWAN cohort, 28% of premenopausal women and 34% of early perimenopausal women reported sleep difficulties, defined as staying asleep as opposed to waking early or difficulty falling asleep.[23.] After adjustment for age, postmenopausal women had more than twice the odds of difficulty falling asleep or waking up several times during the night than premenopausal women. Frequent awakening was also more pronounced among women in surgical menopause (bilateral oophorectomy) compared with premenopause.[23] Fluctuations in FSH may also contribute to sleep difficulties, although the mechanisms are unclear. In the SWAN, both higher FSH levels and more rapid FSH changes were associated with more difficulty sleeping, although other sex hormone levels including E2, T and DHEAS were not linked with sleep after adjustment for FSH.[24] Sleep duration is a risk factor for diabetes. Women with particularly long (>9 h per day) and short (<5 h per day) sleep durations had an increased risk of diabetes.[25] Other analyses found that the U-shaped relationship between sleep duration and diabetes and impaired glucose intolerance persisted even after adjustment for BMI or waist

circumference.[26–28] The mechanisms through which sleep might increase diabetes risk are unknown. Sleep deprivation may increase sympathetic tone, which may depress pancreatic function.[29] More sleep may decrease evening cortisol levels,[30] which may in turn increase insulin resistance.

Owing to the increase in androgenicity, adiposity, sleep disturbance in midlife, and their association with menopausal sex hormone changes, it is logical that glucose levels would also increase.

How female sex hormones act as boon to women for maintain blood glucose.

Important female sex hormones are estrogen & progesterone which are produced by ovaries play a key role in maintaining blood glucose. Accumulating evidence shows that biological sex has a major influence in development of cardiometabolic distrubances, with female being more protected than males. This protection appears to be driven by female sex hormone estrogen as it tends to disappear with onset of menopause.

Insulin resistance is characterized by the inability of circulating insulin to effectively regulate the uptake and/or utilization of glucose by insulin-sensitive tissues and organs. In normal conditions, an increase in blood glucose levels stimulates insulin production from pancreatic β-cells, as well as the inhibition of glucose production in the liver. However, insulin-resistant individuals do not respond to this signaling process, and paradoxically show an increase in both hepatic glucose production and insulin secretion, which can induce or aggravate hyperglycemia.[31] The factors that promote the emergence of insulin resistance include altered insulin signaling, hyperinsulinemia, hyperlipidemia, and obesity. These factors are also associated with chronic low-grade inflammation characteristic of type 2 diabetes mellitus an addition to the regulation of blood glucose levels, insulin is also involved in the regulation of lipid metabolism, particularly in hepatic cells and adipocytes. In the liver, insulin resistance can increase lipogenesis, resulting in the development of nonalcoholic fatty liver disease.[30] Nonalcoholic fatty liver disease involves the accumulation of fat in the liver, and it is recognized as a central component of the metabolic syndrome.[32] Impaired lipid metabolism results in the deposition of surplus lipids in non adipose tissues, which impairs insulin signaling and promotes β-cell hyperplasia.[33] As a result, insulin resistance–induced β-cell glucolipotoxicity interferes with an effective insulin secretion response, further exacerbating insulin resistance as well as glucose and lipid regulation.[33]

Overview of Sex Differences in Insulin Resistance

Men are more susceptible to develop metabolic syndrome than premenopausal women; however, protection in women is significantly reduced when estrogen levels decrease.[34] Consistent with these findings, when compared with premenopausal women, women after menopause and the respective age-matched men present with increased insulin resistance, as measured by homeostatic model assessment–insulin resistance.[35] Menopause is a potential risk factor for developing insulin resistance independent of age, likely due to the reduction in circulating estrogens.[36] In support of this hypothesis, it has been shown that surgically induced menopause increases the risk of developing insulin resistance and metabolic syndrome.[37] Clinical studies show that post-menopausal women are more susceptible than premenopausal women to develop dyslipidemia, an increase in body weight (evaluated through body mass index and waist circumference), and impaired glucose tolerance (as shown by their levels of hyperinsulinemia and increased fasting glucose levels).[36-39]

Association between Insulin Resistance and Low-Grade Inflammatory State and the Role of Estrogens

Organs and tissues involved in glucose metabolism both express and respond to inflammatory mediators.[40] The immune system is significantly influenced by metabolic stimuli and relies on energetic support by inducing catabolism and repressing anabolic processes induced by insulin.[39] Insulin resistance is associated with a low-grade inflammatory state, which may lead to an increased risk of cardiometabolicdiseases.[40] Estrogens are involved in the regulation of metabolic processes related to energy

balance, and can influence inflammatory responses.[41] Many inflammatory components, such as macrophages and monocytes, are activated by estrogen through estrogen receptors expressed in these cells.[41] Furthermore, there is an association between reduced levels of estrogen in post-menopausal women and an increased inflammatory state. Post-menopausal women have increased lymphocyte and monocyte counts, increased expression of proinflammatory cytokines, and increased senescent inflammatory cells, which is usually associated with an improper immunologic function, compared with premenopausal women.[42]

These results are in accordance with other clinical studies that confirm the association between reduced levels of estrogens and an increased proinflammatorystate.[43-44]

Taken together, these findings suggest that estrogens might protect from the development of insulin resistance by both modulating the metabolic processes involved in energy balance and down-regulating and/or repressing inflammation.

Analysis of Sex Differences in Insulin Resistance Using Animal Models

Several mouse models of insulin resistance have been generated, and an extensive description of their characteristics and associated advantages and disadvantages has been published in a review by Nandi et al.[45] Ovariectomies are often performed in animal models to study the underlying mechanisms by which sexual dimorphisms affect biochemical processes.[46] This procedure results in a significant reduction in circulating estrogen levels and represents a viable option to study the impact of female sex hormones in metabolic disorders and insulin resistance in any animal model.[47] Alternatively, treatment with exogenous sex hormones can be used to study the effects of increasing estrogen concentrations. In general, the results from experiments performed in such animal models appear to approximate observations from clinical studies in humans.

Sex Differences in Insulin Resistance in the Pancreas

Hyperinsulinemia is an early indicator of the development of insulin resistance. This condition is established when there is increased insulin secretion by pancreatic β-cells in response to increased blood glucose levels. Impaired lipid metabolism, induced by insulin resistance, leads to adaptive β-cell hyperplasia in a compensatory attempt to increase insulin production. [48] Hyperglycemic and hyperlipidemic conditions, along with a chronically increased demand for insulin, can significantly compromise the function and viability of β-cells.[49]

Ovariectomized C57BL/6 mice develop impaired glucose tolerance when compared with sham-operated controls.[47] Total pancreatic β-cell insulin content, as well as glucose-stimulated insulin secretion from isolated pancreatic islets, is significantly lower in ovariectomized mice relative to their respective sham controls. Supplementation with exogenous estradiol rescues these effects. [47]

The Zucker diabetic fatty rat is a rodent model that presents with sexual dimorphism. Male obese rats become diabetic, and female counterparts remain normoglycemic.[46] Male Zucker diabetic fatty rats have a significant impairment in glucose-stimulated insulin secretion that can be remarkably improved with estradiol supplementation.[50] Male Zucker diabetic fatty rats treated with estradiol also have reduced levels of free fatty acids (FFAs) and triglycerides in the pancreatic islets, suggesting a reduction of lipotoxicity and β-cell failure.[50]

Similar to the Zucker diabetic fatty rats, male New Zealand obese (NZO) mice develop overt diabetes when compared with their female counterparts, which remain normoglycemic.[46] Estrogen deficiency (ovariectomy) in the female NZO mice promotes the development of a diabetic phenotype, with mice showing impaired oral glucose tolerance, and a significant reduction of β-cell mass, when compared with sham-operated females.[51] The observed phenotype in ovariectomized female NZO mice is similar to what is observed in male NZO mice. [51] Ovariectomized NZO mice fed a high-fat and carbohydrate-free diet show significant body weight

gain when compared with sham-operated female controls. Insulin levels are also significantly higher in the ovariectomized group when compared with sham controls, indicating that the loss of estrogens plays a role in the development of insulin resistance.[51] Consistent with these findings, glucose tolerance and insulin sensitivity are impaired in ovariectomized NZO females, compared with the sham-operated controls. Estrogen supplementation improves glucose tolerance, reduces fasting levels of insulinemia, and reduces insulin resistance (homeostatic model assessment–insulin resistance) assessments in ovariectomizedWistar rats, compared with the ovariectomizednonsupplemented controls.[52]

Sex Differences in Insulin Resistance in the Liver

The liver plays an important role in glucose homeostasis as it is a central tissue for glucose production through both gluconeogenesis and glycogenolysis. Hepatic glucose production is mainly regulated by FoxO1, a transcription factor that promotes the expression of glucose-6-phosphatase.[53] Insulin signaling can attenuate hepatic glucose production by inhibiting FoxO1 via downstream Akt activation.[54] In liver-specific FoxO1 knockout mice, glucose tolerance is impaired in both males and females, suggesting that FoxO1 plays an important role in modulating gluconeogenesis.[55] Treatment with estrogen pellets in liver-specific FoxO1 knockout males and ovariectomized females significantly improved glucose tolerance.[55] This suggests that estrogen may signal through the estrogen receptor-α present in hepatic cells. These results are consistent with other studies that show a protective effect of estrogen in terms of hepatic insulin resistance and glucose production by signaling through estrogen receptor-α.[56-58]

Male Wistar rats fed a high-fat diet develop insulin resistance, whereas females do not experience a significant induction.[59] Additionally male, but not female, Wistar rats accumulate hepatic lipid, a hallmark of nonalcoholic fatty liver disease, and have an impaired hepatic insulin response, as measured with homeostatic model assessment–insulin resistance. Lipogenesis also induces an increase in fatty acid synthesis, in turn causing an increase in triglycerides in the form of very-low-density lipoprotein.[60,61] The excess of circulating lipids can have detrimental effects on other tissues and promote CVDs. A study in C57BL/6 mice showed that ovariectomized mice fed a high-fat diet developed insulin resistance along with increased hepatic glucose and triglyceride production. Treatment with estradiol significantly improved insulin resistance and prevented triglyceride accumulation.[60] Similarly, C57BL/6 mice treated with estradiol have reduced lipid accumulation and reduced insulin resistance when compared with untreated male controls.[59]

Finally, the concentration of circulating insulin is regulated by the degradation of hepatic insulin, primarily by the insulin-degrading enzyme in the liver. Enhanced insulin degradation can promote insulin resistance. Ovariectomized C57BL/6 mice present with higher insulin-degrading enzyme levels when compared with the sham controls. Exogenous estrogen supplementation significantly decreases insulin-degrading enzyme levels.[47]

Sex Differences in Insulin Resistance in the Adipose Tissue

Estrogens can prevent the accumulation of visceral abdominal fat in premenopausal women, although this protection is lost following menopause.[62] Consistent with these findings, premenopausal obese women are less prone to develop insulin resistance and altered glucose tolerance than lean age-matched men, hinting that estrogen might exert its protective effect by influencing the pathways that control fat distribution.[63-65]

It is now understood that adipose tissue is an endocrine organ and that adipocytes can directly regulate the pathways involved in energy homeostasis.[64,65] Adipocytes of the intra-abdominal depot of C57BL/6 female mice are more insulin-sensitive than those of male mice as they have significantly enhanced activation of Akt and extracellular signal-regulated kinases compared with males, when stimulated with low doses of insulin.[66] Additionally, female adipocytes highly express genes involved in glucose and lipid metabolism compared with males.[66] Male and ovariectomized female C57BL/6J mice fed with high-fat diet present with

insulin resistance, have increased adipocyte size, and are less protected from adipocyte oxidative stress compared with sham-operated females or ovariectomized females supplemented with estrogen.[67]

Sex Differences in Insulin Resistance in the Skeletal Muscle

Skeletal muscle plays a key role in insulin-stimulated glucose absorption: approximately 85% to 90% of all postprandial glucose uptake occurs at the skeletal muscle tissue.[68,69] Therefore, this tissue is a significant contributor to the development of insulin resistance. Glucose and FFA are transported into skeletal muscle tissue via GLUT4 and CD36, respectively.[70] Hyperlipidemia has been shown to suppress CD36 translocation in skeletal muscle tissue, and consequently heightens the risk of type 2 diabetes mellitus because of impaired lipid metabolism and increased FFA concentration.[71]

Sex differences in insulin action have been investigated by Hevener et al.[71] using Wistar rats infused with a lipid emulsion (liposyn) to increase FFA levels. The liposyn infusion rate to attain a fourfold increase in FFA is approximately one-third higher among female rats when compared with males, indicating that female Wistar rats have a substantially greater FFA clearance compared with males.[71] After liposyn infusion, IRS1 activation is decreased by 30% and class I PI3K activity is decreased by 48% among male rats when compared with female rats, suggesting the potential role of estrogens in improving insulin sensitivity.[71]

A potential determinant of sex differences in insulin resistance in the skeletal muscle tissue is through γABA_B receptor impairment.[72] γABA_B receptor is crucial for the maintenance of glucose-stimulated insulin secretion and glucose homeostasis. Male BALB/c $\gamma ABA_{B1}R$ subunit knockout mice are more susceptible to insulin resistance in skeletal muscle tissue than female BALB/c $\gamma ABA_{B1}R$ subunit knockout mice.[72,73]

Mitochondrial dysfunction may play a role in the development of insulin resistance in the skeletal muscle. Male Wistar rats fed a high-fat diet have significantly more oxidative damage in their skeletal muscle tissues than females.[74.] This is associated with higher mitochondrial biogenesis in males when compared with female controls as a way to compensate the deleterious effects of insulin resistance on oxidative metabolism.[74] Another study investigated the protective effects of estrogen in the skeletal muscle by measuring glucose uptake in the skeletal muscle tissue of male, female, and ovariectomized Sprague-Dawleyrats.[75] Autoradiographic analysis of glucose transport activity in soleus muscle strips from the legs of the experimental rats on a high-fructose diet revealed that the female rats had significantly greater glucose uptake in the skeletal muscle tissue compared with males or ovariectomized female rats, suggesting the presence of sex differences in skeletal muscle tissue insulin sensitivity.[75] Additionally, females showed significantly greater insulin-stimulated activation of IRβ, IRS1 phosphorylation, Akt phosphorylation, and Akt substrate of 160 kDa phosphorylation when compared with males (74). This finding is supported by another study that observed a significant overexpression of GLUT4 among female Wistar rats fed a high-fat diet, when compared with male Wistar rats.[76]

A recent study further elaborated on the mechanism of sex differences in obesity-induced insulin resistance using male and female C57BL/6 mice fed either a high-fat diet or a regular chow diet. [60] Increased insulin sensitivity in skeletal muscle and greater adiposity were associated with significantly greater glucose uptake among the female mice, thus consolidating previously discussed mechanisms of sex differences in insulin resistance in the skeletal muscle tissue. [60] Furthermore, quantification of ectopic diacylglycerol and triacylglycerol levels by liquid chromatography–tandem mass spectrometry analysis revealed significant reductions in the skeletal muscle tissue of female mice, which is likely a result of unhindered FFA metabolism.[60] Estradiol supplementation improved insulin sensitivity in the skeletal muscle tissue with associated enhanced IRS1 phosphorylation and Akt2 phosphorylation in both male and female mice. ([60]).

Sex Differences in Insulin Resistance in the Cardiac Tissue

Insulin resistance is a main driving factor in the development of diabetic cardiomyopathy, a complication of diabetes that can lead to heart failure independent of other cardiovascular risk factors.[77] The hallmark of diabetic cardiomyopathy is diastolic dysfunction.[78]

The effect of estrogen treatment on cardiac function in bilateral ovariectomized, insulin-resistant Wistar rats shows that cardiac ejection fraction and fractional shortening are significantly reduced among ovariectomized rats, indicating that loss of estrogens in an insulin-resistant background results in cardiac contractile dysfunction.[79] Estrogen supplementation in these mice significantly attenuates cardiac autonomic dysfunction, restores systolic blood pressure, and improves cardiac contractile performance.[79] Moreover, Western blot analysis indicates that ovariectomized rats treated with estrogen have significantly higher expression of B-cell lymphoma 2, an anti-apoptotic protein, while simultaneously decreasing expression of bcl-2–like protein 4, a pro-apoptotic protein, thereby highlighting the role of attenuating cardiomyocyte apoptosis among insulin-resistant rats.[79]

A protective role for estrogen in the attenuation of cardiac dysfunction and rescue of insulin action can be seen in studies performed in insulin-resistant H9c2 cardiomyocytes, *db/db* mice, and ovariectomized Wistar rats, whose results are consistent with the existence of female sex differences protecting against insulin resistance in cardiac tissue.[79,80] Additional clinical and preclinical research focusing primarily on sex differences in the pathology of insulin resistance in the cardiac tissue and the respective role of estrogen are needed to further our understanding of the extent of these effects.

Sex Differences in Insulin Resistance in the Endothelium

Insulin promotes endothelial nitric oxide production via signaling through the PI3K-Akt pathway. Nitric oxide induces the vasodilation of blood vessels, thereby increasing blood flow and glucose uptake by the various organs and tissues.[81,82] Nitric oxide also prevents leukocyte adhesion and platelet aggregation as well as smooth muscle cell proliferation.[81,82] Endothelial dysfunction is a feature of insulin resistance and is characterized by a reduced production of nitric oxide by endothelial cells, which can trigger the processes that lead to atherosclerosis and to the development of CVDs.[80,81] Several clinical trials have shown that post-menopausal women have significant endothelial dysfunction compared with premenopausal women, suggesting that depletion of estrogens might be detrimental to the endothelial vascular tissue.[83-85] Studies conducted in women with polycystic ovary syndrome, a condition characterized by hyperandrogenism where most patients present with insulin resistance, show significant alterations in endothelial function.[86,87] These findings suggest that a reduction in estrogens along with insulin resistance could be detrimental and significantly increase the risk of developing CVDs.[88,89] Research conducted on male insulin-resistant Zucker rats treated with estradiol showed a significant improvement in endothelial function by reducing vasoconstriction and increasing vasodilation responses as well as inducing nitric oxide synthase expression.[90] Consistent with these results, ovariectomizedWistar rats treated with estradiol showed a reduced vasoconstrictor response of mesenteric arteries compared with the ovariectomizedWistar rats without estrogen treatment.[91]

DISCUSSION

Ayurvedic observation that Prameha infrequently occurs among women, as emphasized by Acharya Sushruta, represents the underlying insight into the protective function of menstruation for female physiology. This ancient knowledge coincides strikingly with contemporary observations of sex-based disparities in diabetes mellitus (DM) prevalence and presentation. Epidemiological investigations reveal that men in every age group of reproductive years have consistently higher Type 2 DM rates compared to women, pointing towards some

inherent protective mechanism within the female body—a circumstance Ayurveda credits to the routine monthly shodhana (purification) through menstruation.

The protective effect wanes with the onset of menopause, a normal physiological process characterized by the loss of ovarian function and reduction of estrogen levels. The resulting hormonal change precipitates a cascade of metabolic derangements, including elevated insulin resistance, adiposity, sleep disturbances, and inflammatory changes, which together contribute to the increased risk of Type 2 DM in postmenopausal women. Ayurvedic understanding of Prameha as a Vata-Kapha dominant disease finds solace in these physiological alterations since postmenopausal physiology closely resembles Vata imbalance and metabolic volatility.

One of the major themes of this discussion is the action of estrogens, particularly 17β-estradiol, which seem to exert systemic protective actions in all metabolic tissues. Estrogens control glucose metabolism not only by increasing insulin sensitivity in the liver, adipose tissue, skeletal muscle, and pancreas but also by modulating inflammatory responses and maintaining β-cell function. The sudden estrogen deficiency of surgical menopause or ovariectomy models used in both clinical and experimental research repeatedly causes aggravated insulin resistance and glucose intolerance, confirming the hormone's pivotal position in metabolic well-being.

Animal research and clinic studies also support the concept of sexual dimorphism of metabolic reactions. Female mice exhibit greater insulin sensitivity, reduced hepatic fat deposition, and improved skeletal muscle glucose uptake compared to males. These variations essentially vanish following deprivation of estrogen and are re-established with hormone replacement, highlighting the mechanistic connection between sex hormones and Prameha-like states.

Along with biological pathways, female endothelial and cardiac tissues are also insulated against the cytotoxic actions of hyperglycemia and insulin resistance by estrogenic mechanisms. Estrogens enhance endothelial nitric oxide synthesis, suppress vascular inflammation, and augment cardiac contractility—functions altered in insulin-resistant conditions, especially in postmenopausal women.

This integrative perception implies that Ayurveda's viewpoint of Prameha, particularly its sparsity in women with menstruation, is not merely symbolically true but also physiologically real. The monthly cyclical hormonal pattern constitutes an internal homeostatic and detoxifying mechanism that modern science has only just started to fully realize. The convergence between traditional Ayurvedic theory and modern endocrinology here presents a fertile ground for investigating gender-specific preventive measures in diabetes management.

Therefore, identification of the gender gap in Prameha is not so much a conventional perspective but a scientifically feasible model deserving of empirical investigation. It challenges an interdisciplinary solution—integrating Ayurveda, endocrinology, and gender medicine—to reframe how we perceive, avoid, and control metabolic disorders throughout the life cycle of females.

CONCLUSION

The classical Ayurvedic observation that Prameha is rare in women is increasingly supported by contemporary biomedical research. This gender variation, attributed by Ayurveda to the cyclical cleansing effect of menstruation, concurs with modern evidence stressing the protective role of female sex hormones, particularly estrogen, in glucose metabolism and insulin sensitivity.

During the reproductive years, women have a relative metabolic resistance to insulin resistance and Type 2 Diabetes Mellitus—indices of the controlling roles of menstruation, estrogen, and progesterone. But once menopause or surgical hormone deprivation occurs, the protective barrier weakens, and there is greater susceptibility to metabolic dysfunctions, such as Prameha-like states.

Through the incorporation of wisdom from traditional Ayurvedic literature with empirical data from endocrinology, the article highlights the pivotal role of hormonal balance in the pathogenesis and prevention of Prameha. It opens the doors to gender-specific diagnostic, preventive, and therapeutic strategies, and urges more recognition of Ayurveda's sex-specific insights within contemporary models of metabolic health care.

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