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Review

Langhanam in *Ayurveda*; its molecular and metabolic impact on Adipogenesis – A review.

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ABSTRACT:

Introduction: Adipogenesis is a process in which the immature pluripotent mesenchymal stem cells are converted into pre-adipocytes and differentiates into mature adipocytes in adipose tissue. Process of adipogenesis and associated illness shows close resembles to *santharpana* (nourishing therapy) and *santharpana janya vyadhis* (diseases due to excess nourishment) mentioned in Charaka Samhita, and has advocated various types of *langhana* as the treatment. This is a review that shows the relation between the action of *langhana karma* with the advance research methods that causes anti-adipocytic activity. **Materials and methods:** References of *santharpana*, *langhana* and its types from Charaka Samhita, Ashtanga Hridaya and Sushruta Samhita. Different published articles on adipogenesis and anti – adipogenicity with key words, adipogenesis, anti – adipogenicity, PPARγ agonist PPARγ and fasting, PPARγ and exercise, PPARγ and sun exposure were used. Period: from 2013 to 2023. **Result:** While reviewing it is found that types of *langhana* such as *upavasa* (fasting), *vyayama* (exercise) and *atapa seva* (exposure to sun) have significant effects on adipogenesis by changing the expression levels of PPARY gene. Hence, comparison of various types of Ayurvedic *langhana* therapy with several experimental studies, reveals the potential of following basic principles of Ayurveda as well as *langhana* therapy. **Conclusion:** Of the 10 types of *langhana karma* the 3 types have experimentally proven benefits in modifying adipogenesis. The other types have been used by Ayurvedic physicians since generations for almost all diseases as the first line of treatment. Conventional line of treatments has vast side effects when compared with *langhanam* in treating the diseases related to adipose tissue. Hence utilizing the vast knowledge of langhanam in Ayurveda, could open a vast range of significant treatment modalities in addressing adipogenic as well as metabolic related diseases in the present era.

KEYWORDS: *santharpana janya vyadhi, langhanam, adipogenesis, anti-adipogenicity, PPARγ.*

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1. INTRODUCTION

The biological process of conversion of immature pluripotent mesenchymal stem cells into pre-adipocytes and then to mature adipocytes to form adipose tissue is called as adipogenesis. A number of factors such as nutrients, hormones, physical activities etc., affect the process along with the expression and inhibition of several genes, their transcriptional factors and signaling intermediates. The adipose tissue is composed of pre- adipocytes, adipocytes, immune cells, fibroblasts, pericytes, vascular smooth muscle cells and vascular endothelial cells. It is of mainly two types, based on the location as visceral adipose tissue (VAT) or subcutaneous adipose tissue (SCAT). Also, based on its color, structure and function, adipose tissues classified are white adipose tissue (WAT) and brown adipose tissue (BAT). WATs are unilocular cells with a large lipid droplet that synthesis and store triglycerides, mainly found subcutaneously in skin and viscerally in the abdomen. It has reduced vascular supply and maintains energy balance by storage and release of free fatty acids and by heat and energy production. BATs contain multilocular fat cells, present in the interscapular, cervical, axillar, and paravertebral regions. They have many mitochondria with a high rate of fatty acid and glucose uptake and oxidation and are highly vascularized. mostly the metabolic diseases such as hormonal imbalances, impaired insulin sensitivity and their comorbidities are associated with visceral WAT. [1] Recently there is an increase interest in search of a therapy that is capable of modifying the synthesis and functions of adipose tissue, especially WAT to prevent and treat the metabolic diseases.

Adipose tissue dysfunction and associated illness are closely related to *santharpana* (nourishing therapy) and *santharpana janya vyadhis* (diseases due to excess nourishment) mentioned in Charaka Samhita. *Santharpana* is essential to maintain proper nourishment. Overnutrition happens when the quantity of santharpana increases than the prescribed limit. Over nutrition is a form of malnutrition, that arises due to the imbalance of nutrients in food. This imbalance results in excessive accumulation of energy in the form of glucose, triglycerides, glycogen and as fat globules in adipose tissues. The diseases due to over nutrition can vary from childhood obesity to diabetes mellitus and its complications. [2] Charaka Samhita has clearly mentioned about over nutrition and its complications (*santharpana janya vyadhi*) along with its management (*langhanam* – depleting therapy). *langhana karma* (depleting therapy) is having a prime importance as it is indicated as the first line of treatment even in the conditions that requires *santharpana*. This *langhana karma* can be achieved with or without drugs. There are 10 types of *langhana* and they include the four *shodhana* (purification therapy) therapies – *vamana* (emesis), *virechana* (purgation), *niruha basti* (enema with medicated *Kashaya*, oil, honey etc.) and *nasya* (nasal instillation of medicines), *pipasa* (control of thirst), *maruta seva* (exposure to wind), *atapa seva* (exposure to sun), *pachana* (internal administration of *pachana* drugs), *upavasa* (fasting) and *vyayama*(exercise). [3] These measures are prescribed

to the patients after considering their *deha* (strength of the body), *agni* (digestive capacity), *dosha bala* (strength of the *dosha*) and *kala* (time). Each measure has specific indication and methods.

2. AIM & OBJECTIVE:

1. To review the concept of adipogenesis and anti-adiposity.
2. To review the concept of *santharpanam*, *langhana*, its types and indications.
3. To review the relation between the methods and actions of *langhana karma* with advance researches that cause anti adipocytic activity.

3. MATERIALS & METHODS:

Data collection:

1. References of *santharpana*, *langhana* and its types from Charaka Samhita, Ashtanga Hridaya and Sushruta Samhita.
2. Different published articles on adipogenesis and anti – adipogenicity.

Search criteria:

key words with Boolean operators - adipogenesis, anti – adipogenicity, PPARγ gene, PPARγ gene and fasting, PPARγ gene and exercise, PPARγ gene on sun exposure.

Period: from 2013 to 2023.

Total number of research and review articles taken – 15

Included articles – 9

The articles under inclusion criteria were taken and indepth analysis was done.

Table 1: Search strategy used:

Database	Search term used	Inclusion criteria	Exclusion criteria
PubMed	Adipogenesis and PPARγ, PPARγ and fasting, PPARγ and exercise, PPARγ and uv exposure PPARγ and anti-adipogenicity.	Peer – reviewed articles, human and animal studies, cell studies on 3T3-L1 cell lines. Clinical trials and reviews.	Abstracts without full text. Experimental studies related to other gene expressions of adipose tissue.

Observations:

Process of adipogenesis:

Adipogenesis in WAT includes numerous molecular factors such as signaling pathways, epigenetic modifiers and other transcription factors that regulate various genetic expressions. The differentiation of mesenchymal stem cells (MSC) into mature lipid containing adipocytes involves two phases, commitment phase and terminal differentiation phase. Commitment phase involves conversion of MSCs into preadipocytes i.e., they become committed to adipocytic lineage with certain morphological and physiological changes and they lose their ability to differentiate into other cells like osteocytes, chondrocytes. During this phase the genetic expressions in action are PPARγ (the master regulator) Zfp423, BCL6, BMP2, BMP7 etc. In terminal differentiation, transcriptional cascade is activated which includes the expression of genes and adipokines. This results in the transformation of pre adipocytes to lipid filled mature adipocytes. This includes C/EBPα, FABP4, GLUT4, leptin and adiponectin. For the whole process, the expressions of peroxisome proliferator-

activated receptor gamma (PPARγ) and CCAAT-enhancer-binding protein alpha (C/EBPα) are found to have prime involvement. [4] Hence the involvement of genetic expressions of PPARγ is taken for the study in this review.

PPARγ and adipogenesis:

Peroxisome proliferator- activated receptor γ (PPARγ), is a ligand activated transcription factor that is necessary for adipocyte differentiation and regulation of cellular physiology of mature adipocytes. Also, it regulates insulin mediated glucose uptake by peripheral tissues and increases insulin sensitivity. [4] Of the two isoforms of PPARγ, the PPARγ1 and PPARγ2, PPARγ2 is specifically expressed in adipocytes. PPARγ increases insulin sensitivity by enhancing storage of fatty acids in adipose cells. Hence PPARγ has a prime role in adipogenesis along with other positive and negative transcriptional effectors. [5]

Effect of fasting on adipogenesis:

In mice, fasting for about 12 to 48 hours downregulates the expression of PPARγ2 gene for about 80% and about 60% fall in PPARγ mRNA levels in adipose tissue. Also, the level of expression was restored by 50% after feeding for about 24 hours. [6] Hence fasting has a significant role in genetic expressions of adipogenesis.

Effect of exercise on adipogenesis:

Various human and animal experiments have been conducted in the field and among them, 75% human studies shows that different forms of exercises or physical activity enhance the presence of PPARγ levels on adipose tissue. 91% of the conducted animal studies too reveals the same. [7] The expression of PPARγ increases glucose and fat uptake by adipocytes and thereby reduces its load in circulation.

Effect of sun exposure on adipogenesis:

Adipokines are signaling proteins released by adipose tissue. Adiponectin and leptin are some of the adipokines involved in adipogenesis. Adiponectin is involved in GLUT4 mediated glucose uptake and in adipocyte lipid storage. These adiponectin and leptin receptors are down regulated by UV exposure and hence changes adipocyte function. [8, 9]

Limitations of conventional methods:

Developments of targets that stimulate or inhibit PPARγ expression have paved a new way in treating metabolic diseases. One of such development is the discovery of thiazolidinediones, a PPARγ agonist. [10] They act as a transcription factor ligand of PPARγ with its action on modulation of lipid and glucose metabolism, inflammation, atherosclerosis, bone remodeling etc. It acts as insulin sensitizers and are used in the treatment of type 2 DM. [11] However clinical use of the drug is limited due to it side effects. Hence future trend awaits a potential drug or therapy that modulates adipogenesis process with limited side effects. [12]

***Santharpana*m:**

*Santharpana*m (proper nutrition) is essential to maintain proper health. Improper or excess *santharpana*m results in imbalance of dhatus.

Santharpana janya vyadhi:

Excess *santharpana* or overnutrition is due to excess intake of foods that are more unctuous, sweet, heavy to digest and are slimy in nature, new grains, fresh beverages, meat of animals living in water or marshy

land and various pastry preparations, along with a sedentary life style, day sleep etc. [10] All these together results in diabetes, carbuncles, urticaria, itching, anemia, skin diseases, dysuria, anorexia or appetite related complaints, sleepiness, sexual dysfunctions, obesity, laziness, heaviness of the body, adhesion or blockages in the channels as well as sense organs, delusion, various types of oedemas and diseases due to the formation of *ama.* [13]

Management:

Charaka Samhita has advocated various types of *langhana* in managing the diseases related to *santharpana*m. They are various types of *shodhana* (purification therapies), such as *ullekhanam(*emetic therapy), *virechanam(*purgation*), raktamokshanam(*bloodletting*), upavasa* (fasting), *vyayama* (exercises), *dhuma(*inhalation of medicated smoke) and *swedhana* (sudation therapy). [3]

***Langhanam*:**

Langhanam (lightening therapy) is indicated to bring lightness to the body. [14] It also reduces inflammation and improves the digestive capacity. According to Acharya Charaka, there are 10 types of *Langhanam* that can be indicated in various conditions after calculating the *rogi bala* (strength of the patient) and *roga bala* (strength of the disease). [15]

Indications:

Langhanam is commonly indicated in those persons, who suffers from *twak dosham* (skin diseases), *prameha* (urinary diseases including diabetes mellitus), those persons who are habituated to *snigdha* (unctuous), *abhishyandi* (food that causes obstruction to channels like curd) and *bhrimhana* (nourishing) diet. [16]

Types of *langhanam*:

1. *Vamana* (emesis)
2. *Virechana* (purgation)
3. *Niruha vasti* (enema with medicated Kashaya, oil, honey etc)
4. *Nasya* (nasal instillation of medicines)
5. *Pipasa* (water restrain)
6. *Maruta* (exposing to wind)
7. *Atapa* (exposing to sunlight)
8. *Pachana* (using drugs that improves digestion of food and doshas)
9. *Upavasa* (fasting)
10. *Vyayama* (exercise)

Indications of various types of *langhana*:

1. Shodhanam (vamanam, virechanam, niruha vasti & nasyam):

- Indicated in those persons with excessive aggravation *of kapha, pitta and rakta dosha along with vata dosha.*
- With strong and bulky body. [17]

2. With *pachana* drugs:

- To persons suffering from diseases with moderate strength.
- With moderate increase of *kapha and pitta dosha.*
- Diseases such as vomiting, diarrhea, heart diseases, fever, constipation, heaviness of body, nausea, anorexia etc. [18]

3. Pipasa & upavasa:

- Diseases that are indicated for *langhana* with *pachana karma*, but of mild intensity. [19]

4. Vyayama, maruta and atapa sevana:

- Strong person with diseases of moderate intensity.
- Strong person with mild diseases or with little imbalance of dosha. [20]

Pharmaco- therapeutic properties of drugs that causes *langhana*:

Langhana karma can be also brought by therapeutic administration of drugs which possess *gunas(*qualities) that causes *langhana*. They are *laghu*(light), *ushna*(hot), *theekshna*(sharply acting), *vishada*(clearing), *ruksha*(dry), *Sukshma*(subtle), *khara*(rough) and *katina(*hard). [21]

Signs of proper *langhana*:

- Proper elimination of flatus, urine, and feces.
- Lightness of body.
- Clear belching and a feeling of cleanness in heart, throat and buccal regions.
- Absence of drowsiness and exhaustion.
- Perspiration, reappearance of taste, hunger, thirst along with feeling of wellbeing. [22]

Signs of excess *langhana*:

- Pain in various joints.
- Body ache
- Cough, dryness of mouth.
- Complete loss of hunger.
- Anorexia, thirst, weakness of hearing and vision.
- Confusion of mind.
- Fainting, feeling of darkness.
- Loss of digestive power.
- Loss of body weight and strength. [23]

Effect of *langhana karma* on adipogenesis:

Various scientific experimental studies shows that *vyayama* (physical exercise) enhances the presence of PPARγ levels on adipose tissue in humans by 75% and by 91% in animal studies. *Upavasa* (fasting) downregulates the expression of PPARγ2 gene for about 80% and about 60% fall in PPARγ mRNA levels in adipose tissue. *Atapa sevana* (sun or UV exposure) have downregulated the presence of adipokines. Hence *langhana karma* has a significant effect on the process of adipogenesis.

4. DISCUSSION:

Santharpana janya vyadhis mentioned by Acharya Charaka is closely related with the diseases arising due to excess or malfunction of adipose tissue. Hence the treatment methodology employed for *santharpana janya vyadhi's*, i.e. "*langhanam*" could give a hand in preventing and curing diseases related to adipogenesis. The scientific background of *langhana karma* in terms of modern molecular biology is unknown due to its wide therapeutic applicability, significance and complex nature of the *langhana* process as well as human systems. While reviewing it is found that types of *langhana* such as *upavasa* (fasting), *vyayama* (exercise) and *atapa seva* (exposure to sun) have significant effects on adipogenesis. Hence, comparison of various types of Ayurvedic *langhana* therapy with several experimental studies, reveals the potential of following basic principles of Ayurveda as well as *langhana* therapy. There are certain limitations in advocating fasting or physical exercises to all equally. Ayurvedic literatures has immense documentations regarding the indications, contraindications, signs and symptoms of proper and improperly administered therapies etc. At this point the

Ayurvedic treatment modalities paves a way in deciding the exact mode of treatment for individuals with a personalized approach by considering various factors such as strength of the disease, strength of the patient, time period etc. The developing scientific community has only established limited ways of therapies to bring a change in adipogenesis thereby to prevent or cure diseases. Hence, *langhana* therapy can make significant changes in adipogenesis.

5. RESULT AND CONCLUSION:

Of the 10 types of *langhana karma* the 3 types, *upavasa*(fasting), *vyayama*(exercise) and *atapa seva*(sun exposure) have experimentally proven benefits in modifying adipogenesis. The other types have been used by Ayurvedic physicians since generations for almost all diseases as the first line of treatment. Conventional line of treatments has vast side effects when compared with *langhanam* in treating the diseases related to adipose tissue. So, utilizing the vast knowledge of *langhanam* in Ayurveda, could open a vast range of significant treatment modalities in addressing adipogenic as well as metabolic related diseases in the present era.

Abbreviations:

VAT- Visceral adipose tissue

SCAT- Subcutaneous adipose tissue

WAT- White adipose tissue

BAT- Brown adipose tissue

PPARγ- Peroxisome proliferator- activated receptor γ

MSC- Mesenchymal stem cells

BCL6- B-cell lymphoma 6

BMP- Bone morphogenetic protein

C/EBPα- CCAAT/enhancer binding protein alpha

FABP4- Fatty acid binding protein 4

GLUT4- Glucose transporter type 4

mRNA- Messenger Ribonucleic Acid

DM- Diabetes Mellitus

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