

Interplay of Non- Alcoholic Fatty Liver Disease, Male Sexual Dysfunction and Infertility: A Review Article on Both Modern and Ayurvedic Management Approach

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ABSTRACT

Non-alcoholic fatty liver disease (NAFLD) has emerged as a critical public health issue, closely linked to the global obesity epidemic and serving as a significant indicator of metabolic syndrome and cardiovascular disease. In fact, patients who meet specific histopathological criteria for NASH are at the greatest risk for progression to cirrhosis and account for ~15% - 25% of the NAFLD population as a whole. Recent studies indicate that NAFLD affects fertile men, underscoring a strong association between NAFLD and male sexual dysfunction, including infertility. The intricate physiological and molecular mechanisms underpinning this relationship remain incompletely understood. Common risk factors for NAFLD, erectile dysfunction, and male infertility include advanced age, male sex, obesity, obstructive sleep apnea, and conditions associated with metabolic syndrome. In the realm of traditional medicine, *Ayurveda* offers a comprehensive approach to managing NAFLD and male infertility. *Ayurvedic* texts refer to these conditions as *Yakrit vikara* and *Vandhya*, respectively. *Ayurvedic* treatment protocols encompass *Nidana parivarjana* (avoiding causative factors), *Dinacharya* (daily regimen), *Ritucharya* (seasonal regimen), *Samshodhana Chikitsa* (purification therapy), and *Samshamana Chikitsa* (pacification therapy). These holistic strategies aim to restore balance and enhance overall health through dietary adjustments, lifestyle modifications, herbal remedies, and detoxification processes. Emerging evidence suggests that *Ayurvedic* interventions may provide a multifaceted approach to treating NAFLD and associated male infertility. Such treatments are typically less invasive, cost-effective, and have fewer side effects compared to conventional medical therapies. Furthermore, the holistic nature of *Ayurveda*, which emphasizes individualized treatment plans and considers the patient's physical, mental, and emotional well-being, makes it a promising complementary therapy for these conditions.

Key Words *Non-alcoholic fatty liver disease, Male sexual dysfunction, Male infertility, Yakrut vikara, vandhyatwa*

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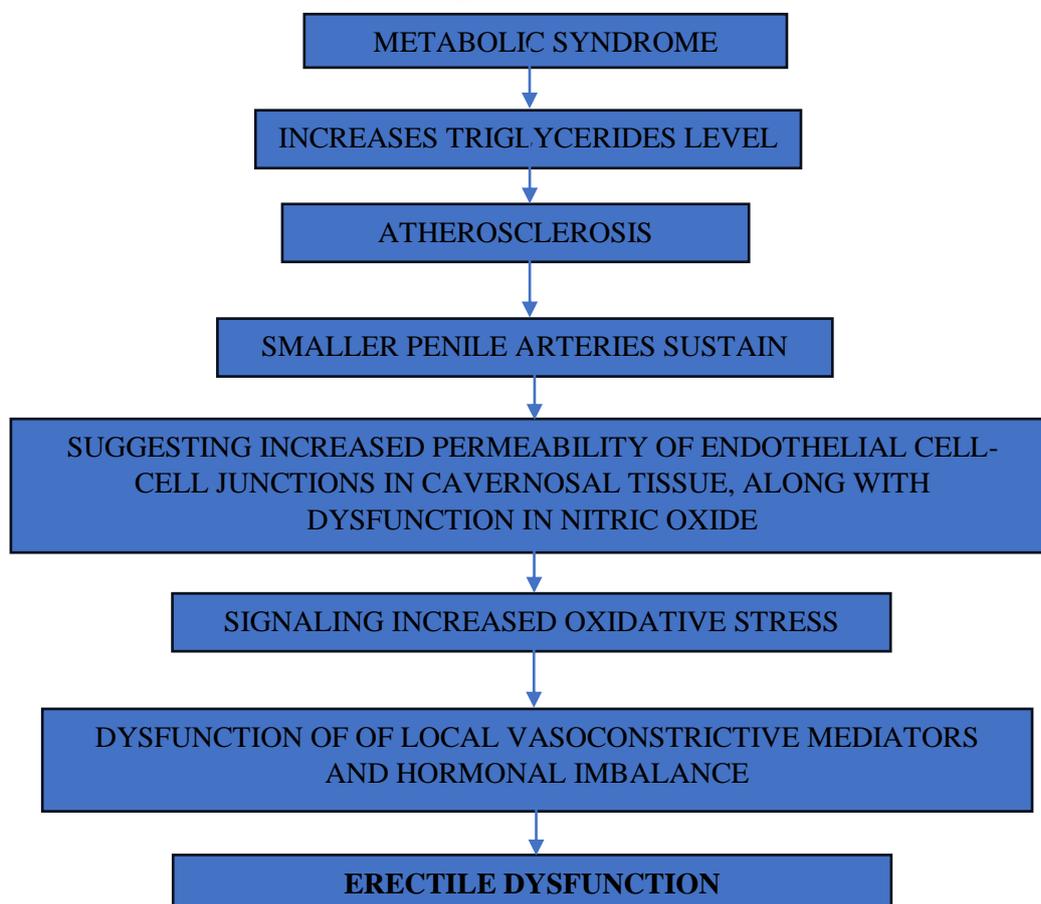
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INTRODUCTION

An elevated triglyceride accumulation in the liver parenchyma without excessive alcohol consumption is the hallmark of nonalcoholic fatty liver disease (NAFLD)¹. It ranges from nonalcoholic fatty liver (NAFL), also known as simple steatosis, to nonalcoholic steatohepatitis (NASH), and was initially reported in 1980². Simple steatosis, which is defined as fat making up 5% of the total weight of the liver without any inflammation, is regarded as a benign disorder. After hepatocyte damage and inflammatory alterations are noticed, NASH is identified; it may then advance to cirrhosis, fibrosis, and, in the end, hepatocellular cancer. Patients who fulfill certain histological criteria for NASH

actually make up around 15%–25% of the total NAFLD population and are most at risk of developing cirrhosis^{3,4}. It is recognized as a hallmark for Metabolic syndrome, a cluster of conditions including insulin resistance, hypertension, dyslipidemia, and central obesity. It is a growing global health concern with potential implications for male sexual function and Infertility. Research suggests that NAFLD can contribute to erectile dysfunction and other sexual health issues like hypogonadism in men. This is believed to be due to the inflammatory and metabolic changes associated with NAFLD, which can impact Vascular and Hormonal function⁵.

Pathophysiology of erectile dysfunction⁶:



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Figure no 1

Vascular endothelium controls a variety of physiological processes involving blood arteries in addition to lining their interior surfaces and acting as a barrier of defense. It regulates platelet aggregation, smooth muscle proliferation, vascular tone, inflammation, and the release and careful balancing of several regulatory variables. A variety of factors can cause aberrant endothelium function, which has been linked to a number of clinical conditions. One of the most prevalent diseases brought on by endothelial dysfunction is atherosclerosis. The bioavailability of endothelium-released vasodilators, primarily nitric oxide, declines during its early stages, tipping the scales in favor of endothelial vasoconstrictors, thickening the intima and media and encouraging the onset of early plaque formation. Narrowing of the arterial lumen occurs when the gradual plaque accumulation reaches around 40% of the arterial diameter. At this stage, obstructive vascular alterations lead to symptomatic vascular disease and the start of the late phase of atherosclerosis. Vasculogenic Erectile Dysfunction is caused by either late cavernosal artery obstruction or early alterations in endothelium-mediated smooth muscle relaxation. Penile erection is primarily a vascular process⁷. Furthermore, Nitric Oxide generated by

the endothelium supports the maintenance of erection, and when Nitric Oxide availability declines, more Erectile Dysfunction occurs(Fig.1). Endothelial dysfunction has been proposed recently as one of the early causes linked to the formation of liver fat and eventual liver disease. Similar to other vascular endothelial cells, liver sinusoidal endothelial cells play a critical role in anti-inflammatory and antifibrotic activities. Furthermore, it has been shown that decreased Nitric Oxide generation contributes to the development of NAFLD and its eventual progression to advanced liver disease, such as cirrhosis, by aggravating and intensifying the inflammatory condition of the liver. Endothelial Nitric Oxide synthase (eNOS) malfunction has been observed in individuals with non-alcoholic fatty liver disease (NAFLD) according to recently published human data, and animal studies show that eNOS deficiency exacerbates the early stages of NAFLD. The insulin signalling pathway is responsible for eNOS activation, hence IR, which is frequently observed in NAFLD, ED, and MetS, may eventually be a major source of eNOS dysfunction. Since NAFLD has been found to be a separate risk factor for CVD, there's a good chance that the original hepatic endothelial dysfunction played a part in this relationship⁸.

PATHOPHYSIOLOGY OF HYPOGONADISM⁹:

INCREASED INSULIN LEVELS RESULTING FROM IR



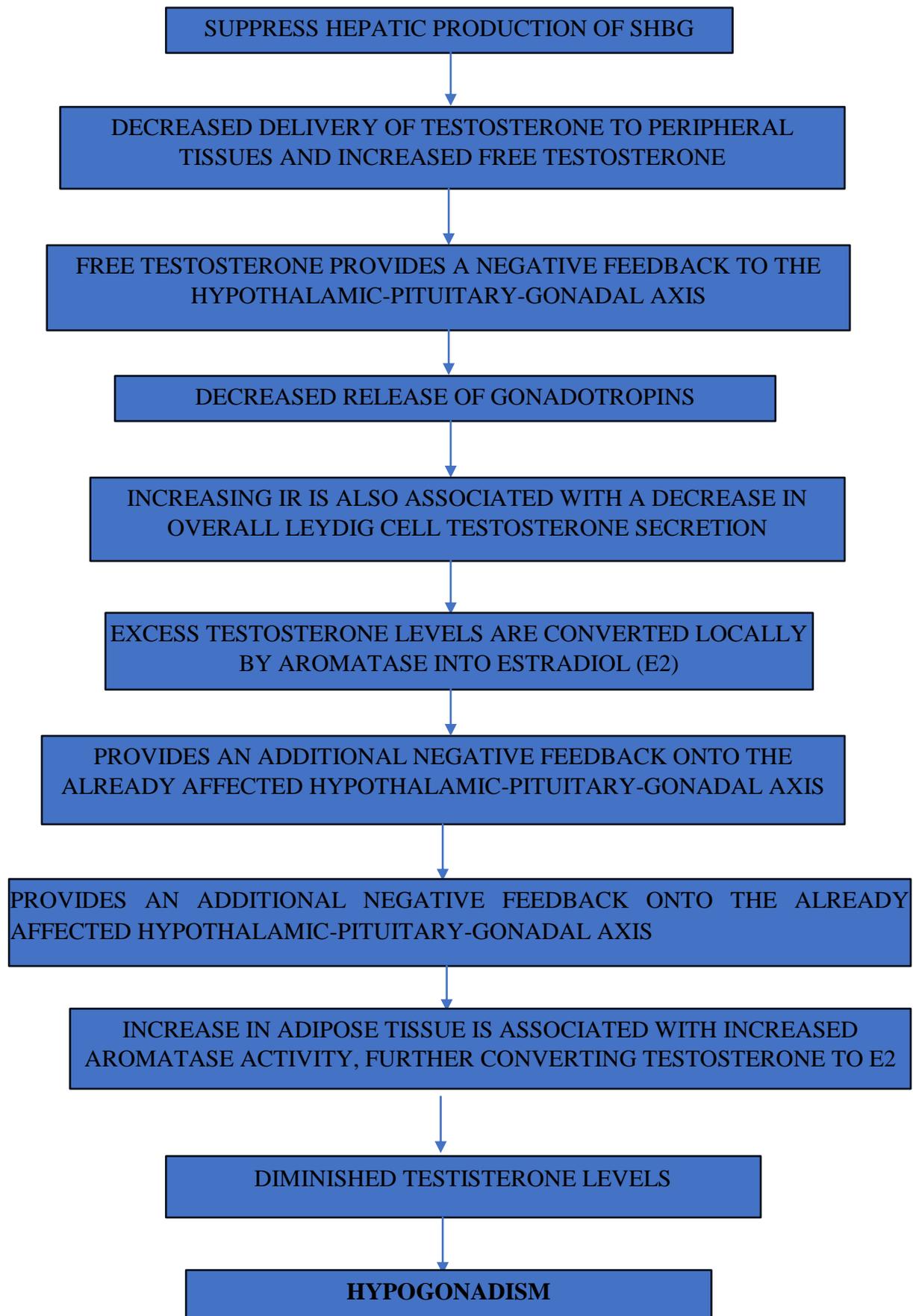


Figure no. 2

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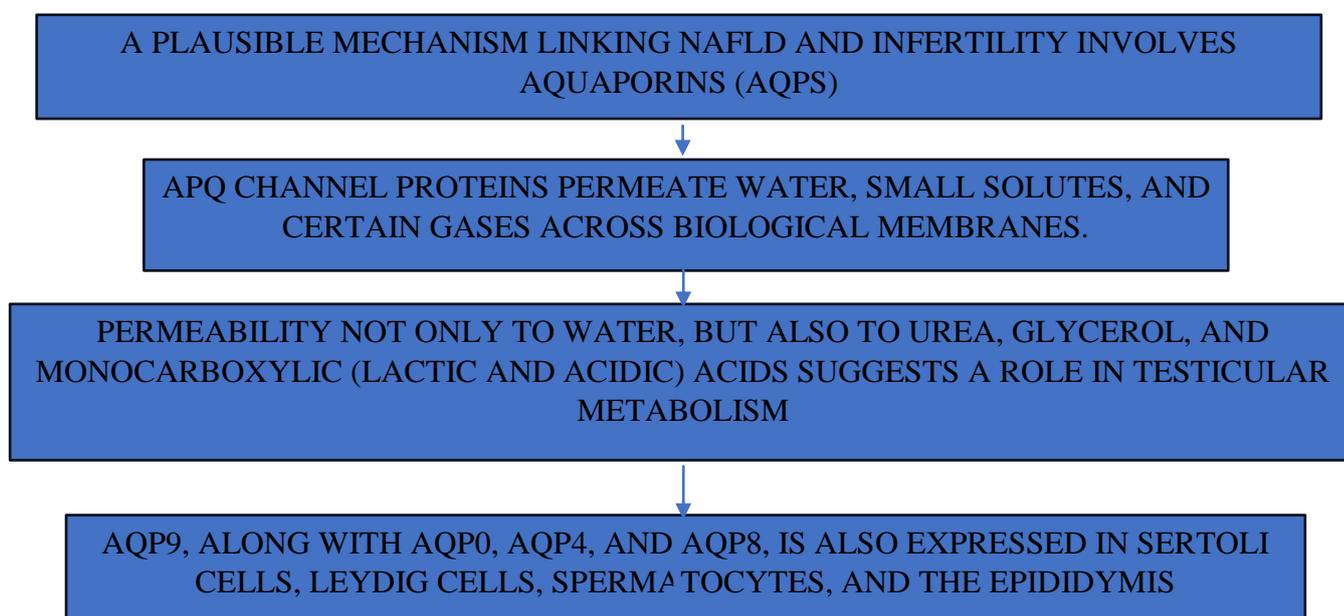
The precise pathophysiological pathways are still unclear, despite the well-established links between T deficit and MetS and T2DM. Some insight is provided by Insulin Resistance-potentiated increases in aromatase activity and obesity-related reductions in SHBG. Elevated insulin levels brought on by IR inhibit the liver's synthesis of SHBG, which leads to a reduction in Testosterone transport to peripheral tissues and an increase in free Testosterone. The hypothalamic-pituitary-gonadal axis receives negative feedback from free Testosterone, which eventually reduces gonadotropin release¹⁰. A reduction in total Leydig cell Testosterone secretion is similarly linked to increasing Insulin Resistance. Furthermore, aromatase locally converts excess Testosterone levels into estradiol (E2), adding to the hypothalamic-pituitary-gonadal axis' existing negative feedback loop. Moreover, elevated aromatase activity linked to an increase in adipose tissue further converts Testosterone to E2, resulting in lower

Testosterone levels and a preference for the deposition of visceral fat. The low Testosterone levels brought on by the aforementioned molecular mechanisms might affect a person's metabolic profile, increase visceral fat, and potentially aggravate Erectile Dysfunction linked to obesity. According to recent clinical and animal research, Testosterone may also contribute to the beneficial effects on hepatic lipid metabolism by converting to E2 and activating the estrogen receptor α thereafter¹¹. This low Testosterone levels will lead to a condition called as Hypogonadism(Fig. 2).

PATHOPHYSIOLOGY OF INFERTILITY:

Growing evidence indicates that NAFLD may also be linked to Male infertility. The condition can affect sperm quality, motility and DNA integrity, potentially reducing a man's ability to conceive. Underlying factors, such as oxidative stress, chronic inflammation and hormonal imbalances, may play a role.

HEPATOCTYTE AND SERTOLI CELL AQUAPORINS¹²:



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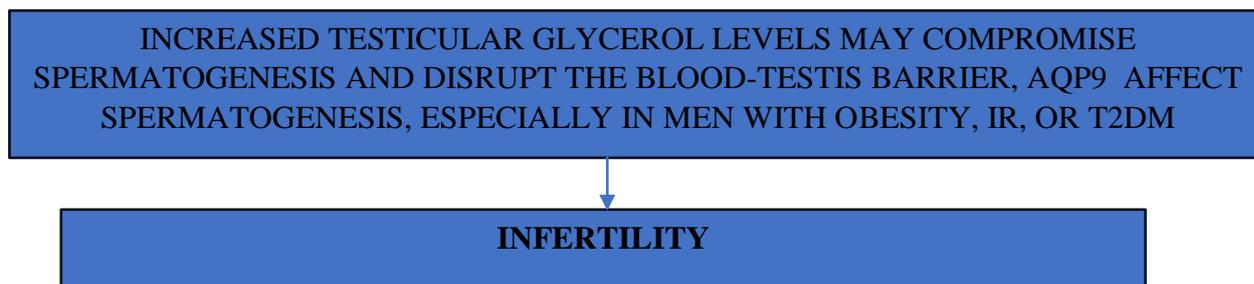


Figure 3

A complex interaction of genetic, environmental, behavioural, and hormonal variables can lead to fertility issues. Research suggests that abnormal semen characteristics may be a sign of a man's general health. It is also common knowledge that many men who have comorbid diseases are infertile since their poor health and required medical treatments might impair the quality of their semen. It has been shown that obesity, type 2 diabetes, and hypertension negatively impact semen parameters, particularly sperm quality and total ejaculate volume¹³. The Charlson Comorbidity Index (CCI) compared the scores to semen characteristics that were measured. There was an inverse relationship between the severity of comorbidity and semen quality. Men with higher CCI scores (>1) had poorer scores for morphology, total sperm count, sperm motility, and semen volume. It is not unexpected that males with genitourinary, endocrine, nutritional, or metabolic issues had far greater incidence of anomalies in their semen. Semen abnormalities were also more common in males with CVD (hypertension, peripheral vascular disease, cerebrovascular disease, and non-ischemic heart disease). T2DM, obesity, and hyperlipidaemia—components of MetS—are further linked to male

infertility by all of these results(Fig. 3). Furthermore, NAFLD has been linked to endocrine diseases, CVD, and concomitant metabolic disorders. It may also have an impact on semen quality, according to new research¹⁴.

NAFLD AND IMPAIRED REPRODUCTIVE FUNCTION¹⁵:

Although it is unknown if NAFLD affects male reproductive function, it is known that serum Testosterone is necessary for healthy testis development, germ cell differentiation, and appropriate spermatogenesis. According to clinical research, men with NAFLD had far lower blood Testosterone and SHBG levels than men in good health. Additionally, a multivariate analysis revealed that while there were no significant variations in semen volume or shape, changed sperm parameters—such as concentration, count, and total motility—were substantially correlated with non-alcoholic fatty liver disease (NAFLD)¹⁶.

SHARED RISK FACTORS AND COMORBIDITIES¹⁷:

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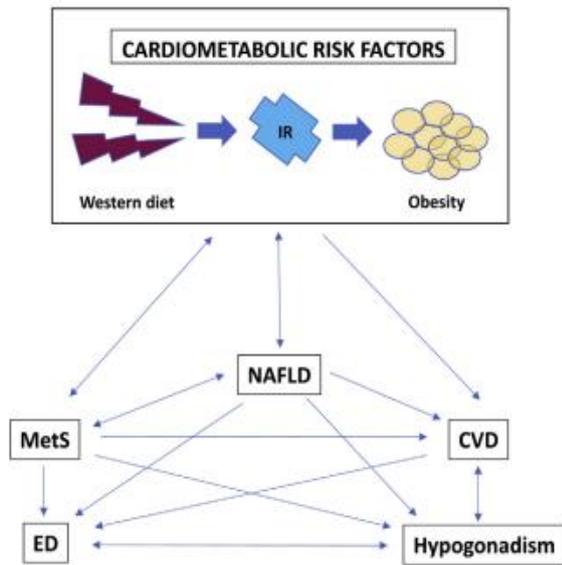


Figure 4
NAFLD, erectile dysfunction, and male infertility (Fig. 4) often share common risk factors, such as:

- Older age
- Male sex
- Obesity
- Obstructive sleep apnea
- Metabolic syndrome such as insulin resistance, T2DM, and dyslipidemia
- Sedentary lifestyle¹⁸.

Understanding these interconnected factors is crucial for comprehensive management and treatment strategies.

INVESTIGATIONS FOR NAFLD¹⁹:

- Ultrasound
- NAFLD liver fat score
- MRI PDFF
- MRS
- Steato-test
- CAP Scan
- Liver Biopsy

INVESTIGATIONS FOR MALE INFERTILITY²⁰:

- Semen analysis
- Investigations to diagnose microbial conditions such as UTI, STD's, male accessory gland infections
- USG & Colour doppler study of testis
- Serum FSH, LH, Testosterone levels
- Anti sperm antibody test, hypo osmotic swelling test
- CT scan or MRI of pelvis
- Chromosomal studies
- Testis biopsy & vasography
- Fine needle aspiration 'mapping' of the testes

MANAGEMENT²¹:

MODERN APPROACH FOR NAFLD:

- Thiazolidinediones:
 - Rosiglitazone
 - Pioglitazone
- Antioxidants
- Hepato-protective agents:
 - Pentoxifylline
 - Telmisartan
 - L- carnitine
 - Vitamin E

MODERN APPROACH FOR MALE INFERTILITY²²:

- Recombinant FSH
- Human Chronic Gonadotropin (HCG) hormone
- Human-menopausal Gonadotropin releasing hormone (GnRH)
- Clomiphene citrate

AYURVEDIC APPROACH:

- **Proper Dietary Management²³:**

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✓ *Pathya: Yava, Mudga, Ghritam, Takra, Dugdha, Masha, Godhuma, Tandula, Madhu, Kukkutanda, Mamsa rasa.*

✓ *Apathya: Katu, Amla, Lavana, Kshara, Atiushna, Viruddha anna, Asatmaya anna.*

▪ **Life Style Advice:** *Dinacharya, Rutucharya, Ratricharya, Trayupstambha, Sadvritta, Achara Rasayana, Ashtanga Yoga.*

▪ **Panchakarma:** *Snehana, Swedana, Virechana, Basti.*

▪ **Single drugs:** *Amlaki, Haritiki, Gokshura, Shilajit, Yashtimadhu, Bhumiamlaki, Kiratikta, Haridra, Guduchi.*

▪ **Formulations:**

a. *Choornam²⁴: Hinduvachadi choornam, Vaiswanara Choornam, Mahadrakshadi choornam.*

b. *Kashaya²⁵: Vasaguduchyadi Kashaya, Phalatrikadi Kashaya, Drakshadi Kashaya.*

c. *Yoga: Dhatriphaladi yoga*

d. *Vati: Shilajatu Vataka*

e. *Ghrita²⁶: Dadimadya Ghrita, Draksha Ghrita.*

CONCLUSION:

An Ayurvedic method can be very beneficial for male infertility, male sexual dysfunction, and non-alcoholic fatty liver disease (NAFLD). The core causes of these illnesses can be addressed with *Panchakarma* treatments, particular Ayurvedic formulations and herbs, lifestyle adjustments, and proper nutritional control. Maintaining liver health and improving reproductive function may be achieved by eating a balanced diet, keeping to daily and seasonal

schedules, and regularly engaging in detoxification. In order to help with the general treatment of these illnesses, Ayurvedic herbs and formulations offer focused assistance for purification, regeneration, and augmentation of vitality.

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