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Short Review

The Pathophysiology and Management of NAFDL in Post-menopausal Women: An Updated Short Review

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Abstract

Non Alcoholic Fatty Liver Disease (NAFDL) is a condition in which an individual suffers from an accumulation of fat in the liver. This is a disease condition with a multifactorial etiology. Some potent causes of such conditions are altered thyroid condition, abnormal metabolism in the body due to aging or menopause, or any other hormonal imbalance. Most of these causes are regulated by genetics, lifestyle, and environmental factors. Menopause comes with tremendous hormonal turmoil in the human body and brings various abnormal conditions that significantly divert from physiological conditions. One such condition that comes along with menopause in women is NAFLD. Also, the progression of NAFDL is more in post-menopausal women than in premenopausal women. This review aims to comprehend and understand from the existing literature if the prevailing NAFLD condition worsens and aggravates in women with menopause or remains unaffected. This short review briefly discusses the pathophysiology of the onset and progression of NAFDL in post-menopausal women. Lifestyle restrictions, diet, proper monitoring, and medications and supplementations are the only ways to manage NAFLD in post-menopausal women. A

detailed and better understanding of NAFDL, its onset, progression, and association with the physiological condition of post-menopausal women is necessary to better manage and treat the NAFDL condition in post-menopausal women.

Keywords
Non Alcoholic Fatty Liver Disease; menopause; management; lifestyle; diet; medications; postmenopausal women

1. Introduction

Menopause is the term used to denote the end of reproductive age in women when the regular menstrual cycle stops. The natural menopausal age for women is 45-50 years globally. Studies reveal that with menopause, the estrogen level decreases in circulation, which is associated with the worsening of non-alcoholic fatty liver disease (NAFLD) in women [1]. This causes dysregulation of the metabolism of the body [2]. Estrogen is associated with regulating several metabolic processes in our body, and estrogen deprivation affects various physiological processes in our body adversely, which may be responsible for the ill effects of estrogen deprivation on hepatic health. Premenopausal women have been reported to be in a better condition than post-menopausal women in the context of the severity of NAFLD. Studies claim that NAFLD enhances the risks for cardiovascular disease and type II diabetes in post-menopausal women and thus increases morbidity in menopausal women [1]. NAFDL is a condition in which fat accumulates in the hepatic tissue, and as a result, the liver's normal function gets hampered [3]. NAFDL is a pathogenic condition of the liver which is associated with altered metabolism of fat in the body. If the state goes unrecognized, undiagnosed, and untreated for a long, it may worsen to steatosis of the liver, cirrhosis of the liver, and even cause death. Certain genetic predispositions and other pathological conditions of the body, like hypothyroidism, diabetes etc., have been found to be linked to the occurrence and progression of NAFDL [4]. Menopause, which comes with a vast hormonal turmoil in the women's body, has been reported to be intimately associated with causing, worsening, and progression of NAFDL and thus significantly contributes to the morbidity of post-menopausal women [1, 2]. Women with polycystic ovaries also suffer from hormonal imbalance and are susceptible to NAFDL [5, 6].

Adequate awareness and alertness may help in the early detection of NAFDL conditions in women who have menopause. Women should undergo screening for NAFDL immediately following their menopause. Timely detection of NAFDL helps the proper and effective management of the condition and also yields good results with treatments. Hormone replacement therapy (HRT) has been reported to be significantly effective in alleviating the need for NAFDL in post-menopausal women [7]. Dyslipidaemia is recognized as an associated ailment with NAFDL due to an altered pattern of fat metabolism [3], and HRT is reported to help treat the condition of dyslipidemia along with NAFDL in post-menopausal women [7]. Published literature related to menopause and NFDL have been primarily searched on the internet in international databases of scientific literature like Web of Science, Pubmed Central, Science Direct, Research Gate, Google Scholar, etc., 260 papers were found to be relevant to the theme of this review were selected

based on the inclusion criteria like relevance, period or year of study, etc. and 130 full papers were downloaded and studied among which the information from some 50 have been considered for this review. Papers published before the year 2005 were excluded. Articles with a complete focus on the pathophysiology of NAFDl in post-menopaual women were considered. A few papers with allied details of NAFDL but not in women were also referred.

2. Menopause and the Liver Function

Studies reveal that with menopause, the female hormone estrogen level decreases. Estrogen is known to significantly impact the hepatic health [8, 9]. These all are known to be the risk factors for the development and progression of NAFDL [7]. Gut microbiota and butyrate are also known to be associated with NAFDL. In post-menopausal women, the gut microbiota also gets altered due to altered hormonal levels following menopause [10]. Decreased estrogen levels are known to cause several physiological changes in the body, and many of them significantly adversely affect the liver [11]. Reducing estrogen levels is also reported to promote the aging of the immune system. This, in simple words, may be described as an increase in the various inflammatory and proinflammatory cytokines that occur due to lower estrogen levels, leading to the enhanced inflammatory state in post-menopausal women [12]. Administration of estrogen in post-menopausal women may improve the conditions of liver disorders, including NAFDL. The primary beneficial effects of estrogen on liver disorders are that estrogen helps to inhibit fibrogenesis in hepatic tissue, protects the structures and functions of hepatic mitochondria, enhances innate immunity, reduces cellular and immunological aging, and mitigates oxidative damage in the liver by promoting antioxidant effects therein [11].

3. Dyslipidemia, Obesity, Menopause, and NAFLD

Estrogen is associated with the maintenance of a good lipid profile. Estrogen lowers the level of LDL and increases the level of HDL. Post-menopausal women have been reported to have an increased level of triglycerides and cholesterol [13]. Also, post-menopausal women have been reported to be prone to gain weight, dyslipidemia, and redistribution of fat in their bodies. They have been written to have higher BMI than premenopausal women [9]. Studies show that though men are more susceptible to developing NAFDL, women beyond middle age have more incidence of NAFDL [11, 14]. Aging in post-menopausal women is also recognized as a factor responsible for altered fat metabolism and the development of NAFLD [14]. Studies conducted in mice model shows that ovariectomized mice suffered more severe steatosis of the liver for being estrogen deficient. The same estrogen-deficient mice are also reported to have increased body weight, abdominal fat weight, and increased serum triglycerides [10]. Several genes are associated with the coding of various peptide molecules directly related to fat metabolism and the development and progression of NAFDL [4, 15]. These genes and different transcription factors are affected and regulated by certain hormones like the thyroid, insulin, and estrogen. Thus, these hormones are connected to the regulation of metabolism in our body. With menopause, there occurs a total imbalance of hormones in the body. Among these, the level of estrogen starts going down significantly following menopause. All these hormones crosstalk and interplay to influence fat metabolism in the liver. Their imbalance together contributes to the onset and progression of dyslipidemia and NAFDL in post-menopausal women. Menopause causes a reduction in estrogen

levels, which leads to the accumulation of fat and causes obesity in post-menopausal women. Studies show that obesity is associated with NAFDL [16]. With a decrease in the level of estrogen following menopause, there occurs an increase in the level of circulating androgen. These hormonal changes lead to altered lipid metabolism in women following menopause [17]. Dysregulated lipid metabolism culminates in situations like adiposity, obesity, and NAFDL. Fat metabolism dysregulation impacts the body's fat mass, fat-free mass, metabolism of fatty acids, and different aspects of energy metabolism [17]. Studies show that basal metabolic index (BMI) increases in post-menopausal women, which increases the risk of cardiovascular risk in post-menopausal women [18]. Interestingly, menopause is found to be linked to altered levels of various types of lipids in circulation. Lipids circulating in the blood like apolipoproteins, lipoproteins, low-density lipoproteins (LDLs), high-density lipoproteins (HDL), and triacylglycerol (TG) etc., get altered with menopause [19]. All these may play together to bring about the altered mobilization of fat in the liver and accumulation of fat in the liver, leading to NAFDL in post-menopausal women. Women with menopause are at higher risk of developing NAFDL. Studies show that the progression and development of NAFDL increases in women with menopause [1]. The prevalence of NAFDL and other pathogenic conditions associated with fatty liver is reported in post-menopausal women compared to that in premenopausal women [1].

Among various metabolic factors that affect NAFDL in post-menopausal women, central obesity and insulin resistance have been reported as the key players [20]. Post-menopausal women are known to have increased insulin resistance [21]. Post-menopausal women are at higher risk of developing NAFDL due to the reduction of the protection imposed by estrogen. With menopause, the estrogen level goes down, which enhances the risk of developing NAFDL. Reduced estrogen also affects various metabolic pathways in a women's body, which, in a combined manner, contributes to the development of NAFLD in post-menopausal women [22]. Thus, NAFDL is more prevalent in women who belong to post-menopausal age. Studies report that post-menopausal women with NAFDL had higher BMI, higher levels of AST, ALT, GGT, triglycerides, fasting glucose, lower HDL cholesterol, and larger waist circumference. Also, post-menopausal women with NAFDL reportedly have hypertension and diabetes [23]. Together, these alter various metabolic factors affecting the pathophysiology of NAFDL in post-menopausal women.

4. Diagnosis, Prevention, and Treatment of NAFDL in Post-menopausal Women

NAFDL may go unnoticed and undetected as it doesn't give any significant early-stage symptoms. Hence, intermittent checking and superficial ultrasonography of the upper abdomen is recommended for recognition of the condition of the liver [4]. In post-menopausal women, Regular check-ups and diagnostic tests for other physiological parameters are needed. With the cessation of the menstrual cycle, women have several health ailments. Hence, timely evaluation, early detection, and proper treatment and management may help to prevent the worsening and further progression of these health ailments, including NAFDL in post-menopausal women. Also, any associated condition like diabetes, cardiovascular disorder, dyslipidemia, or hypothyroidism may be recognized timely with regular testing. This will help understand the pathophysiology and underlying mechanism of NAFDL in post-menopausal women. Treatment protocols may be specific for specific health conditions of the individual. The primary treatments include lifestyle modifications, medications, hormone replacement therapy, treatment of other associated health

ailments that may aggravate the condition of NAFDL, diet, exercise, etc. [1, 24, 25]. Antioxidants have been reported to have hepatoprotective potential [26]. Antioxidants help to reduce oxidative damage and stress by removing free radicals [26]. Antioxidant-rich vegetables and fruit are highly recommended for post-menopausal women to protect against oxidative stress-mediated complications in NAFDL (Figure 1). Also, a diet low in carbohydrates and lipids is recommended (Figure 1). Studies suggest that exercise and weight reduction in post-menopausal women may be beneficial in dealing with the NAFDL condition [27]. Resistance training is expected to prevent the unfathomable distribution of fat and associated problems like NAFDL [27]. Certain nutritional factors have been reported to be beneficial against NAFDL conditions, especially in post-menopausal women. Choline, soy Isoflavones, and probiotics have been investigated and recommended to manage NAFDL in post menopausal women [28] effectively.

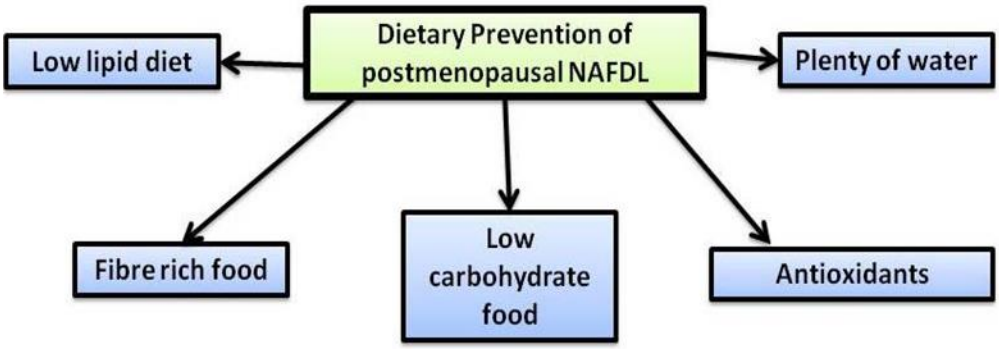

Figure 1 Dietary prevention of post-menopausal NAFDL.

5. Implications of Estrogen Deprivation on the Onset, Progression and Severity of NAFLD

With menopause, estrogen level goes down. Studies show estrogen deprivation impacts the onset, progression, and severity of NAFDL in post-menopausal women. Thus, the NAFDL in post-menopausal women is known to be linked to the decreasing estrogen level in circulation in them [29]. A higher incidence of NAFDL is reported in men and post-menopausal women than in premenopausal women. In men, aging leads to hypogonadism and lower production of testosterone, which is known to be correlated to the incidence of NAFDL in aging men [30, 31]. The risk of aging men developing NAFDL and lowering testosterone in them has been reported in many studies [31]. Low serum testosterone is thus known to be associated with the risk of NAFLD in men, unlike in post-menopausal women with type 2 diabetes mellitus [31]. NAFDL is a metabolic disorder, and studies report that the prevalence of NAFDL is higher in patients with metabolic disorders than in regular [32]. Estrogen is also said to play a complicated role in regulating the metabolism of lipids and glucose. Androgens are also known to contribute to the principle of lipid and glucose metabolism but in a complex way similar to estrogen [33]. Studies report the protective effects of estradiol in hepatic diseases in women. Estradiol, the prevalent circulating form of estrogen, is known to be secreted by the ovaries primarily in premenopausal women, and the hormone level goes down in post-menopausal women [34]. Estradiol is also produced from other tissues, but ovaries are the primary sources. Studies show that women after menopause have an increased risk of cardiovascular diseases, increased insulin resistance, dyslipidemia, glucose intolerance, and hypertension. Also, women in the reproductive age group have been reported to be at lower risk of NAFDL than men in the same age group. Whereas,

women in the post-menopausal age group have been said to be more vulnerable in developing NAFDL and progression of NAFDL and other complications associated with NAFDL, including fibrosis of the liver and development of hepatic carcinoma compared to that in men of the same age group [14, 35-38]. The protective effect of estrogen on hepatic health is extensively reported in the literature [39]. Hence, though there are not enough studies to reveal the underlying mechanism of the association of estrogen deprivation in post-menopausal women with onset, progression, and severity of NAFDL, studies available firmly establish the fact that estrogen has a protective role on hepatic health and lower level of estrogen in circulation following menopause in women is associated with the enhanced risk for onset, progression and severity of NAFDL in post-menopausal women. Studies also reveal that a long duration of estrogen deprivation in post-menopausal women with NAFDL increases the risk of developing hepatic fibrosis [40]. Decreased estrogen level is reported to cause increased LDL cholesterol, triglyceride, insulin, etc., and the deprivation of estrogen is known to favor the development of hepatic steatosis [41]. Estrogen is thus adapted for potential therapeutic application in addressing the occurrence and severities of NAFDL in post-menopausal women. Besides estrogen, androgen is also used in HRT [39].

6. Conclusion

There occurs tremendous hormonal turmoil in the women's body during menopause, leading to myriads of degenerative and deteriorative health alterations [41, 42]. Among these, one significant hepatic deteriorative condition often reported to onset during or worsen following menopause is NAFDL. With proper knowledge of the condition and early detection and treatments, the state of NAFDL may be prevented and, if already existing, be prevented from worsening. Hence, spreading awareness may help to understand the pathophysiology and handling techniques for NAFDL in post-menopausal women. Besides, HRT and proper diet, lifestyle management, and exercise are essential for reducing and maintaining low body weight in post-menopausal women. This helps manage and prevent the onset and progression of NAFDL in post-menopausal women.

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Author Contributions

Mr. AM: Literature search and Writing. Ms. BP: Writing. Dr. DG: Conceptualization, literature search, writing and reviewing.

Competing Interests

The authors have declared that no competing interests exist.

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