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Review

Support Needs and Coping Strategies in Non-Alcoholic Fatty Liver Disease (NAFLD): A Multidisciplinary Approach to Potential Unmet Challenges beyond Pharmacological Treatment

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Abstract: Non-alcoholic fatty liver disease (NAFLD) is the most frequently occurring chronic liver disease, affecting approximately 25–30% of the adult general population worldwide. NAFLD reflects excess hepatic accumulation of fat in the absence of increased alcohol intake, and, due to its close association with obesity, is frequently referred to as the 'hepatic manifestation' of metabolic syndrome. Indeed, a high percentage of individuals with NAFLD present with a combination of the cardiometabolic comorbidities that are associated with the metabolic syndrome. In addition to its well-established link with the metabolic syndrome and increased risk for cardiovascular disease, NAFLD has also been associated with certain mental health issues (e.g., depression and stress). Although this link is now being increasingly recognized, there are still unmet needs regarding the holistic management of patients with NAFLD, which could further contribute to feelings of social isolation and loneliness. The latter conditions are also increasingly reported to pose a substantial risk to overall health and quality of life. To date, there is limited research that has explored these issues among patients with NAFLD, despite existing data which indicate that perceived loneliness and isolation may pose an additional health risk. Notably, many features associated with NAFLD have been related to these concepts, such as perceived stigma, fatigue, stress, and confusion regarding this diagnosis. As such, this review aimed to assess such potential problems faced by patients with NAFLD, and to explore the possibility of unmet support needs which could lead to perceived social isolation. Moreover, the importance of a compassionate approach towards such patients is discussed, together with potential coping strategies. Future research directions and the need for a multidisciplinary approach are also highlighted.

Keywords: non-alcoholic fatty liver disease; NAFLD; stigma; fatigue; stress; obesity; loneliness; isolation; compassion; coping

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1. Introduction

Often referred to as a 'silent epidemic' [1], non-alcoholic fatty liver disease (NAFLD) is now the most frequently occurring chronic liver disease globally, affecting approximately 25–30% of the adult general population worldwide [2]. This prevalence increases further among adults with obesity, affecting up to 90% of such individuals [3,4]. Caused by excess accumulation of fat in the liver, which is not related to increased alcohol intake, NAFLD is often viewed as the 'hepatic manifestation' of metabolic syndrome [5]; a condition which denotes a cluster of obesity-related conditions, including dyslipidaemia, hypertension, and type 2 diabetes mellitus (T2DM) [6]. Indeed, around 85% of individuals with NAFLD exhibit components of the metabolic syndrome [7]. NAFLD may progress to non-alcoholic steatohepatitis (NASH) and even more advanced liver disease [2], including cirrhosis and hepatocellular carcinoma. In this respect, a recent paper observing liver cancer trends on the island of Crete, Greece, reports a continued increase in NAFLD in this region over the past 25 years, with NAFLD representing an important risk factor for hepatocellular carcinoma [8]. In addition when modelling the disease burden in various European countries, alongside Japan, China, and the USA, reports indicate that cases of advanced liver disease resulting from NAFLD are likely to rise at least 2-fold by 2030 [9]. Furthermore, NAFLD represents a significant risk factor for cardiovascular disease (CVD) [7]. An increasing body of evidence also indicates an association between NAFLD and mental health problems, such as depression, anxiety, and chronic stress, which may have further clinical implications for the management of patients with NAFLD [10].

To date, there is no established specific pharmacological treatment for NAFLD, with lifestyle changes in the form of diet and exercise to aid weight loss representing the typical intervention for the first line management of this condition [11]. In this context and as NAFLD prevalence keeps increasing, the support needs of individuals with NAFLD may often remain unnoticed, which could lead to additional problems, such as loneliness and social isolation. Furthermore, there appears to be a lack of information and limited understanding regarding NAFLD as a chronic health condition [12,13], which could result in the emergence of feelings of isolation.

Within this framework, although literature addressing NAFLD and potential perceived isolation is currently limited, several features associated with NAFLD are related to this concept, such as perceived stigma, fatigue, and stress [14–16], as well as certain common mental health problems (e.g., depression). In addition, perceived loneliness and social isolation have been shown to exhibit associations with a number of cardio-metabolic disorders linked to NAFLD, including obesity, T2DM, metabolic syndrome and CVD [17–20].

The present review summarizes potential challenges faced by patients with NAFLD and highlights the possibility of unmet support needs which could result in perceived social isolation of such patients. The latter merits further investigation in the context of the holistic management of NAFLD. Moreover, this review discusses the importance of a compassionate approach for the care of individuals with NAFLD, and explores potential coping strategies.

2. Methods

Although this work represents a narrative review rather than a systematic review, a predefined search strategy was formulated, utilising relevant search terms in relation to NAFLD, metabolic syndrome, related cardio-metabolic disorders (e.g., obesity and T2DM), awareness, fatigue, stigmatisation, loneliness/social isolation, and coping strategies. The searched databases included both PubMed and Google Scholar. After removing duplicates and screening, key papers were reviewed in full and were included as relevant to the scope of this review, as presented in the following sections. Selected key relevant studies included in this narrative review are summarized in Table 1.

Table 1. Selected key studies on links between non-alcoholic fatty liver disease (NAFLD) and features which may represent potential unmet needs among patients with NAFLD.

Study [Reference]	Country	Study Design/Cohort	Concept	Outcome/Main Findings
Alemany-Pages et al. (2020) [12]	Portugal	Cross-sectional N = 30 (53% female) Median Age: 65	Awareness	Low awareness of NAFLD both as a disease entity, and in terms of its progression to end-stage liver disease or its association with other metabolic conditions.
Morill et al. (2021) [21]	Mexico	Mixed methods: Cross-sectional N = 194 (100% female) Median Age: 47 Semi-structured interviews N = 26 (100% female)	Awareness	Low awareness of risk factors for liver disease. Knowledge regarding liver disease was mainly centered on cirrhosis. The findings from both the quantitative and qualitative study identified that sources of information for NAFLD were mainly friends, family, and media. Interviews revealed a misperception related to NAFLD risk, namely that liver disease was only caused by high alcohol intake.
Wieland et al. (2015) [22]	USA	Self-administered questionnaire N = 302	Awareness	Low awareness of NAFLD among individuals at high metabolic risk. Most paticipants reported interest in learning more about NAFLD.
Tincopa et al. (2021) [23]	USA	Qualitative N = 29 (51.7% female) Age: 51.7% $\geq$50 years	Awareness	Patients showed awareness of lifestyle interventions as the main therapy for NAFLD, but expressed a gap in knowledge regarding the condition. The presence of social support and competing medical comorbidities were the most consistent facilitators and barriers to lifestyle change.
Newton et al. (2008) [24]	UK	Cohort study N = 120 (57% male) Mean Age: 53	Fatigue	Fatigue is a significant problem in NAFLD, and is associated with impaired physical function. Fatigue among patients with NAFLD does not seem to be related to either the severity of underlying liver disease or insulin resistance.
Jung et al. (2019) [25]	Korea	Observational N = 112,797 (51.5% female) Mean Age: 40	Depression and Anxiety	Both the presence and severity of NAFLD are significantly associated with symptoms of depression.
Youssef et al. (2013) [26]	USA	Cross-sectional N = 567 (67% female) Mean Age: 48	Depression and Anxiety	Symptoms of depression and anxiety are common in patients with NAFLD.

Table 1. *Cont.*

Study [Reference]	Country	Study Design/Cohort	Concept	Outcome/Main Findings
Weinstein et al. (2011) [27]	USA	Retrospective Patients with NAFLD: N = 184 (69.4% female) Mean Age: 46.7	Depression and Anxiety	Higher prevalence of depression in patients with NAFLD and hepatitis C, compared with patients with hepatitis B and members of the general population.
Kim et al. (2019) [28]	USA	Cross-sectional N = 10,484 (female: 51.2%) Mean Age: 47	Depression and Anxiety	Higher prevalence of depression among individuals with NAFLD compared to those without.
Choi et al. (2021) [29]	South Korea	Retrospective Cross-Sectional N = 25,333 (56.2% male) Mean Age: 47	Depression and Anxiety	Severe steatosis is significantly related to both state and trait anxiety in patients with NAFLD.
Han (2020) [30]	Korea	Cross-Sectional N = 17,726 (50.6% male) Mean Age: 43.9	Stress	An indication of an increased risk of NAFLD (by 1.3 times) in individuals with increased perceived stress was identified.
Kang et al. (2020) [31]	Korea	Cross-sectional N = 171,321 (50.1% male)	Stress	Independent association between higher levels of perceived stress and a greater prevalence of NAFLD.
Li et al. (2016) [32]	China	Cross-sectional N = 2367 (100% male) Mean Age: 36.65	Stress	High occupational stress and high personal strain identified as independent risk factors for NAFLD.
Carol et al. (2022) [15]	Spain	Cross-sectional N = 144 (52% male) Mean Age: 64	Perceived Stigma	Perceived stigmatisation is common among patients with NAFLD. This is independent of disease stage, and is associated with impaired quality of life.
Lazarus et al. (2021) [11]	Global	Based on retrieval of tweets globablly: 16,835 tweets for NAFLD 2376 tweets for non-alcoholic steatohepatitis (NASH)	Pereived Stigma	Retrieved tweets mostly indicated an unmet information need, without any clear signs of stigma. However, the negative content of obesity tweets was recurrent.

Table 1. *Cont.*

Study [Reference]	Country	Study Design/Cohort	Concept	Outcome/Main Findings
Kim et al. (2020) [20]	Korea	Cross-sectional Community based population: N = 8097 (66.6% female) Age range: 30–64 years Hospital based population: N = 2006 (58% male) Age range: 30–80 years (To avoid possible confounding effects from age differences, 1861 participants aged 65 years and older were excluded from final analyses).	Loneliness	Smaller social networks are associated with metabolic syndrome which could be partly due physical inactivity.
Henriksen et al. (2019) [33]	Norway	Longitudinal N = 26,990 (55% female) Mean Age: 45	Loneliness	Loneliness may be an important factor associated with an increased the risk for metabolic syndrome. The effect of loneliness on metabolic syndrome is mediated via depressive symptoms.
Jung & Sikorski (2019) [19]	Germany	Cross-sectional N = 1000 (55.2% male) Mean Age: 56.4	Loneliness	Greater levels of loneliness were reported by respondents with higher levels of depression, higher internalized weight bias, and experience of discrimination.
Ida et al. (2020) [18]	Japan	Cross-sectional N = 558 (57.3% male) Mean Age: 73	Loneliness	Glycaemic fluctuations and insulin use are associated with social isolation and being homebound among older patients with diabetes.
Brinkues et al. (2017) [34]	Netherlands	Population-based cohort study N = 2861 (51% male) Mean Age: 60	Loneliness	Several aspects of structural and functional characteristics of the social network are associated with newly and previously diagnosed type 2 diabetes.
Valtorta et al. (2016) [35]	UK	Systematic Review	Loneliness	Findings suggest that deficiencies in social relationships are associated with an increased risk of developing coronary heart disease and stroke.
Cene et al. (2022) [17] [36]	USA	Systematic Review	Loneliness	Evidence is most consistent for a direct association between social isolation, loneliness, and coronary heart disease and stroke mortality.

Table 1. *Cont.*

Study [Reference]	Country	Study Design/Cohort	Concept	Outcome/Main Findings
Brenton-Peters et al. (2021) [36]	New Zealand	Systematic Review	Compassion	Self-compassion interventions tailored to weight management outcomes demonstrate efficacy with increasing self-compassion post-intervention.
Austin et al. (2021) [37]	Netherlands	Systematic Review	Compassion	Feasibility and acceptability of compassion-based interventions among individuals with chronic conditions were rated high by participants. The review also revealed reduced anxiety and depression. Participants also indicated greater acceptance of their condition, reductions in feelings of loneliness, and improvements in emotion regulation skills.
Ramalho et al. (2021) [38]	Portugal	Cross-sectional Participants with chronic disease: N = 278 (85.6% female) Mean Age: 42.20	Compassion	Results highlight the crucial role of self-compassion skills and the ability to perceive others as compassionate, in loneliness and quality of life. This finding applies to individuals either with or without a chronic condition.
Funuyet-Salas et al. (2021) [39]	Spain	Cross-sectional N = 307 (60.7% male) Mean Age: 54.8	Coping	Diabetes and obesity were associated with lower quality of life in patients with NAFLD. Obesity was also associated with more passive/avoidance coping. Such strategies predicted lower quality of life than active strategies.
Yasmeen et al. (2015) [40]	Pakistan	Qualitative Study N = 275 (66.9% males) Mean Age: 44	Coping	Significant differences in the coping strategies utilised by cardiac and renal failure patients were identified. Renal failure patients used physical coping strategies more, whereas cardiac patients were more likely to use psychological and behavioral coping strategies
Raposa et al. (2016) [41]	USA	Cross-sectional N = 77 (53.2% female) Mean Age: 24.52	Coping	Prosocial behaviour moderates the effects of stress on positive affect, negative affect, and overall mental health, suggesting that helping behaviour could represent an important method for coping with stress.
Lazar & Eisenberger 2022) [42]		Cross-sectional N = 91 (60.4% females) Mean Age: 20.84	Coping	Findings demonstrate that engagement in prosocial behaviour following a stressor can help to downregulate physiological stress responses.

3. Awareness and Understanding of NAFLD

The history of NAFLD is reported to date back to the 19th century, whereby literature from this time describes an association of fatty liver with malnutrition, sedentary lifestyle, alcohol and unhealthy food intake [43]. Indeed, the related lifestyle and clinical risk factors were often posited in a way that has been described as 'less compassionate' than the way in which we may view such factors today [43]. It was not until the mid-1980s that the term NAFLD was suggested by Schaffner and Thaler [44], whilst there remains some confusion as to what the disease actually represents and how it should be treated.

Although the importance of patients with NAFLD understanding their condition in order to aid their self-management is widely recognized, there seems to be a certain lack of awareness among such patients, and indeed among the general public, regarding NAFLD and its related health issues [12,16]. As such, these patients are often confused when faced with the NAFLD diagnosis, and may believe that liver failure is the main health risk, whereas CVD is in fact the leading cause of mortality in this patient population [13].

Recently, following a consensus of international experts, the possible benefits of renaming NAFLD to metabolic-associated fatty liver disease (MAFLD) have been discussed [45,46]. It is argued that the use of more positive wording, such as 'metabolic-associated' rather than 'non-alcoholic', might help to detract from the potential negativity associated with the latter, and that this renaming might assist in increasing the current understanding of this highly prevalent condition [45,46]. Indeed, early reports suggest awareness of this condition could be improved by such a name change [9].

As argued by Francque et al. [16], a further problem with the term NAFLD, is that it 'tells you what it [NAFLD] is not, instead of telling you what it is'. Thus, this viewpoint offers further support for a name change to MAFLD, in order to provide a broader picture of the condition, and to avoid the risk of inappropriate treatment strategies [16]. Likewise, Shiha et al. [47] argue that because the name NAFLD focuses on excluding alcohol, it leads to misunderstanding since this criterion is insufficient for the diagnosis of the condition. This may in turn have an impact on effective communication due to oversights regarding the issue of metabolic dysfunction and metabolic health awareness [47].

However, there is some debate regarding the potential renaming from NAFLD to MAFLD, in part since there exists a vast amount of literature on NAFLD from the past 40 years, and to transfer this to a 'novel' disease name, such as MAFLD, might be problematic [44].

What seems to be a clear issue, and one that is also worthy of further attention, is that there is still a lack of awareness and some confusion regarding the NAFLD diagnosis. This appears to apply to both patients and the general public, despite the value that comprehensive disease awareness can have for better self-management activities [12,16]. This may be due, at least in part, to the fact that certain aspects of the NAFLD pathophysiology are still not fully understood, which is likely to also have an impact on the information that is passed onto patients [16].

Of note, Shiha et al. [47] emphasise the importance of understanding patients' perspectives in order to identify unmet needs. It is reported that patients often refer to delays in diagnosis which may reflect a lack of NAFLD awareness, and also an inability of healthcare professionals to communicate and relay information in a clear manner which can be easily understood by the patient [47]. Accordingly, it has been suggested that it may be useful to identify specific NAFLD information needs of certain high-risk populations (e.g., people with T2DM), as this could assist in the promotion of NAFLD awareness and health promotion strategies [12]. Interestingly, in a study designed to assess levels of awareness, knowledge and sources of information in relation to NAFLD among women of Mexican origin, researchers identified that knowledge relating to liver disease centred around cirrhosis and that there was very low awareness with regard to risk factors related to NAFLD [21]. It was further revealed that individuals participating in this study believed that liver disease could be caused only by high levels of alcohol. When asked about information sources, participants revealed that they relied mainly on family, friends, and media. Thus, it was

concluded that such low levels of NAFLD awareness require substantial efforts to educate the general population and that this should also be incorporated into T2DM educational programmes [21].

Further issues arise regarding diagnosis of a disorder whereby there is currently no established specific pharmacological treatment, and where clinicians' attitudes to discussing the management of obesity may vary considerably [13]. As suggested by Berry & Kotha [13], failure to communicate effectively when applying the label of NAFLD during diagnosis, may lead to patients leaving the consultation with the opinion that they are likely to encounter liver failure. Thus, it is suggested that NAFLD represents an ethical dilemma, not only because of its association with obesity, but also due to confusion regarding its diagnosis, lack of specific treatment, and difficulties surrounding physicians' attitudes when discussing obesity [13]. In addition, there is also marked diversity among the patients with NAFLD due to risk elements, including socioeconomic status, ethnicity and genetic factors. As such, Berry & Kotha [13] further suggest that strategies for communication should be tailored to the individual patient, since unless patients can gain a better understanding of NAFLD and the related CVD risk, changes to lifestyle and their overall management may prove unsuccessful [13]. Indeed, this is an important factor to consider, given that, as aforementioned, CVD related events represent the leading cause of NAFLD-related mortality [13].

Adding to the relevant body of evidence, another study by Wieland et al. [22] sought to identify awareness of NAFLD among participants both with and without risk factors for NAFLD. This study revealed a worryingly low awareness of NAFLD, even among patients with major risk factors. Furthermore, 73% of participants reported an interest in learning more about NAFLD and receiving NAFLD education at a patient centred level. Accordingly, these authors highlight the need to raise public awareness regarding NAFLD, especially among individuals who are at high risk, in order to optimise prevention and care strategies [22]. Similarly, in a qualitative study by Tincopa et al. [23], semi-structured interviews were conducted to identify behaviour, knowledge and attitudes among 29 individuals with NAFLD. Results emerging from this study indicated much ambiguity relating to both the aetiology and diagnosis of NAFLD. In addition, although most participants were aware that the main therapy for NAFLD involves weight loss and exercise, many showed low levels of concern regarding their NAFLD diagnosis. In this study, identified facilitators and barriers regarding lifestyle changes included social support, clinical comorbidities and low motivation. As such, Tincopa et al. [23] suggest the implementation of tailored interventions on a personalised basis, which would take into account individual barriers and facilitators to lifestyle changes [23].

Overall, it should be highlighted that patients diagnosed with NAFLD may lack the necessary knowledge regarding their condition and may feel confused regarding who to turn to for advice. This lack of awareness and information may lead to feelings of isolation, particularly as there is no specific pharmacological treatment for NAFLD, with management focusing on lifestyle modification.

4. Fatigue and NAFLD

NAFLD typically presents either without any, or with very few physical symptoms (e.g., some right-sided abdominal pain). As such, in early, uncomplicated stages of NAFLD, there are generally no substantial symptoms and no apparent NAFLD-related quality of life impairment. However, if NAFLD progresses, quality of life may become impaired (e.g., as a result of increasing fatigue) [16]. Indeed, when NAFLD patients initially report physical health issues, these often seem to be related mainly to fatigue, which has been reported as a significant problem for patients with NAFLD (e.g., also linked to persistent daytime sleepiness) [24,48].

Notably, fatigue remains a complex and poorly understood issue in NAFLD, with the liver playing a role to its pathogenesis, whilst other factors might also be involved, such as hypothalamic pituitary adrenal (HPA) axis dysfunction [49]. In general, fatigue is

naturally difficult to define due to the underlying interactions of biological, behavioural and psychosocial factors [49]. Contrary to extreme tiredness which usually subsides following sleep, fatigue represents an overwhelming form of tiredness which typically cannot be eliminated by sleep [16].

Alongside fatigue, it is also noted that symptoms of depression can be present in patients with NAFLD. This relationship may be due to changes in serotonin levels which relate both to depression and fatigue. However, although treatments for depression may be prescribed, there is little evidence to suggest that such treatments are effective in treating fatigue [49]. Indeed, it appears that fatigue in patients with NAFLD may be managed more effectively via exercise and weight loss, whilst pharmacological treatments seem to lack reliability in decreasing fatigue [49].

In the management of patients with NAFLD, fatigue is an important issue to address, since it will almost certainly affect their overall well-being and quality of life [49]. Moreover, fatigue can result in social withdrawal, negative feelings, self-blame and a reduction in coping strategies [16]. These factors can further lead to depression, which may lead to the adoption of unhealthy behaviours (e.g., over-eating) as a strategy for overcoming such negative feelings, thus creating a vicious cycle [16]. Of note, a study by Newton et al. [24] explored whether fatigue was associated with impaired physical function and potential underlying causes. In this study, compared to a control group, fatigue was significantly higher in individuals with NAFLD, who also demonstrated less physical activity over the course of the past six days. However, this study did not identify an association between fatigue and either insulin resistance or the severity of liver disease [24]. Thus, it was concluded that fatigue is a major issue in patients with NAFLD, and that this association might be indirect. To elucidate these links, further studies aimed at investigating potential factors which might be related to both fatigue and NAFLD (e.g., adipose tissue inflammation) could be of value [24]. Indeed, a better understanding of the underlying mechanisms linking fatigue and NAFLD may assist in the provision of more targeted therapeutic strategies [50]. This would also aid in addressing the risk of social isolation and negative feelings which may emerge among patients with NAFLD as a result of chronic/persistent fatigue.

5. NAFLD and Mental Health

In addition to fatigue, individuals with NAFLD may encounter mental health issues and loss of self-esteem, which can also have a profound impact on health-related quality of life [48]. Historically, there has been a limited focus on potential relationships between NAFLD and mental health, although a growing body of evidence has highlighted a number of associations between NAFLD and prevalent mental health problems, including depression, anxiety and chronic stress [10].

Depression is highly prevalent worldwide, constituting a leading cause of years lived with disability [51], whilst it is further associated with a number of physical conditions (e.g., obesity, T2DM, metabolic syndrome and CVD) [52,53]. Interestingly, potential links have also been reported between depression and NAFLD severity [25], with positive associations between the intensity of depression and certain NAFLD-related factors (e.g., body mass index and hypertension) among patients with NAFLD [26]. Furthermore, a higher prevalence of depression has been identified in these patients, in comparison to the general adult population [27]. Notably, depression has also been highlighted as an independent risk factor for the development of NAFLD [28]. Similarly, a recent retrospective cross-sectional study demonstrated a significant relationship between severe steatosis and both state and trait anxiety in patients with NAFLD [29].

Overall, there is increasing evidence of a bidirectional relationship between NAFLD and such mental health conditions, with reports suggesting that NAFLD may increase the risk of depression and anxiety, and that depressed individuals might be more likely to develop NAFLD, independently of other comorbidities [54]. However, it is noted that there

may be other underlying factors in relation to these associations, including links between depression and/or anxiety and unhealthy lifestyle behaviours [10].

Regarding psychosocial stress, it is of importance that a recognised relationship exists between chronic stress and increased risk of cardio-metabolic conditions, such as obesity, T2DM, hypertension and CVD [55,56]. Although less research has investigated specific links between NAFLD and psychosocial stress, available studies have also identified chronic stress as an independent risk factor for NAFLD [30–32], pointing to evidence that NAFLD may represent a stress-sensitive disorder. Of note, stress involves responses that are both biological and behavioural in nature, resulting in activation of the HPA axis that leads to increased levels of cortisol and pro-inflammatory biomarkers which could also be involved in the development of NAFLD [10].

Based on the available evidence, it is now suggested that a feed-forward cycle may exist between NAFLD and certain prevalent mental health conditions, with NAFLD potentially representing a contributing cause of depression, anxiety, and/or chronic stress, whilst such mental health conditions might also promote NAFLD [10]. Given the potential clinical implications of these links for the management of patients with NAFLD, further investigations should be directed towards studying the exact underlying mediating pathways.

6. Perceived Stigmatisation

Stigma can be defined as ' . . . as a social process, experienced or anticipated, characterized by exclusion, rejection, blame or devaluation that results from experience, perception or reasonable anticipation of an adverse social judgment about a person or a group . . . ' [15]. In this context, NAFLD may have a further impact on the individual because of the concept of perceived stigma. This may relate to issues, such as obesity-related stigma, and/or feelings of guilt associated with the presumed association of liver disease with alcohol and/or drug abuse [15,16].

Stigmatisation and obesity are well-documented, with assumptions reported along the lines that obesity is solely associated with lack of motivation and self-discipline [13]. Indeed, variations in physicians' attitudes to obesity have been highlighted, with some physicians exhibiting negativity and strong weight bias [13]. This can promote stigmatisation, since such attitudes may be communicated to patients (even unconsciously), and can further have a detrimental effect on the therapeutic relationship [13].

A study by Carol et al. [15] reported that perceived stigma was highly prevalent among patients with NAFLD, affecting all studied domains (i.e., stereotypes, discrimination, shame, and social isolation). Given this prevalence of perceived stigmatisation, the findings of this study suggest that the human and social rights of individuals with NAFLD may be affected with an impact on the quality of life in association with the above-mentioned domains [15]. Such findings should be viewed as a 'warning sign', due to the sensitivity of this issue among patients with NAFLD, and should be brought to the attention not only of researchers, but also of healthcare professionals, patient associations and relevant policy makers [15].

Interestingly, as patients with NAFLD may feel stigmatised by both the wording 'non-alcoholic' and the NAFLD association with obesity, together with the fact that 'stigma' often emerges on social media outlets, Lazarus et al. [11] examined how stigma regarding NAFLD/NASH and obesity manifested on Twitter. The findings of this study demonstrated that most tweets in association with NAFLD/NASH referred to an unmet need for information, rather than to issues of stigma. However, recurrent tweets regarding negativity and obesity were evident [11]. Thus, given the association of NAFLD with obesity, this study raises concerns regarding the likelihood of an increase in NAFLD-related stigma in the future, and further suggests that interventions aimed at reducing stigma on social media platforms should be considered in relationship to the broader management of NAFLD [11].

Of note, Shiha et al. [47] have described painful stories from patients following a NAFLD diagnosis regarding the way in which NAFLD is viewed among their friends and

family. This often leads to the patient remaining silent, and not disclosing their diagnosis to those close to them [47]. Furthermore, elements of self-blame (typically associated with fears that the condition may be seen as self-inflicted) may lead to a lack of motivation in terms of seeking help and support, thus posing a further risk for social isolation and loneliness. In this context, Shiha et al. [47] suggest that stigma in relation to a health condition can be sub-divided into self-stigma and public stigma, and highlight the negative effects of stigmatisation on quality of life and self-esteem (e.g., the fear of stigma leading to self-denial and treatment avoidance following diagnosis. Due to this the potential growth in stigmatisation in relation to a NAFLD diagnosis, Shiha et al. [47] also discuss the possible benefits of removing the reference to alcohol from the diagnosis by renaming NAFLD to MAFLD, arguing that this can help to prevent perpetuation of stigmatisation, bring comfort to patients most in need, and encourage a more patient-centred approach.

Similarly, a consensus statement by Lazarus et al. [57] argues for the importance of consideration of the implications of stigma, further drawing attention to the fact that people with NAFLD and other co-existing chronic conditions are likely to experience several interacting forms of stigmatisation. Thus, the need for stigmatisation to be acknowledged when considering treatment and prevention strategies for NAFLD is stressed, further arguing that the involvement of high-profile persons diagnosed with NAFLD could have an important impact in terms of promoting NAFLD awareness and reducing associated stigma [57]. Accordingly, it is also suggested that effective non-stigmatising messages should be targeted towards a number of audiences, including healthcare professionals, relevant policy makers and the general public, and that the media should also be involved in awareness tools and strategies [57].

It is evident that, since both obesity and liver disease frequently lead to stigmatisation, it is likely that patients with NAFLD could also be increasingly subjected to such stigmatisation [15]. Therefore, this issue is worthy of further attention within clinical practice in order to also prevent a potential impact on promoting loneliness and social isolation among this patient population.

7. Loneliness and Social Isolation

Although difficult to define, loneliness is often referred to as a discrepancy between an individual's desired and actual social relationships [58,59], whilst social isolation represents a situation of having few or infrequent social connections [17]. Despite modern technology and social networking tools, both loneliness and social isolation are recognized as increasing global issues [14,58]. Indeed, even before the start of the COVID-19 pandemic, it was reported that almost half of the older adults in England (46%) experienced loneliness [60]. Interestingly, a study by Jovicic & McPherson [60] further reported there was a certain amount of reluctancy among general practitioners (GPs) in terms of raising this issue with their patients, as they felt uncomfortable with their ability to openly discuss the concept. Likewise, a study by Kharicha et al. [61] identified that individuals who experienced loneliness did not consider the primary care setting as being equipped to deal with such an issue due to the lack of physical symptoms.

However, as reported by the World Health Organization (WHO) [62], social connections are crucial to both physical and mental health, with the impact of loneliness and social isolation on health and mortality being similar to well-established risk factors, such as smoking and obesity [62]. It should be highlighted that perceived loneliness can be highly distressing for an individual, and may have serious physical and psychological health-related implications, particularly as people experiencing loneliness or social isolation may not seek suitable health information and treatment/management of existing conditions [63].

To date, there is a lack of direct evidence/research relating to the association of loneliness and NAFLD, which is mostly based on indirect evidence regarding loneliness and social isolation in individuals with NAFLD-associated diseases/disorders. Indeed, a study by Kim et al. [20] showed a positive association between higher prevalence of

metabolic syndrome and small social networks, potentially attributed to lack of physical activity in socially isolated individuals. Since this study identified a mediating effect of lack of physical activity on the positive association between metabolic syndrome and small social networks, developing strategies to increase physical activity in individuals with small social networks were suggested as a possible solution to this issue [20].

Moreover, in attempting to determine whether loneliness increases the risk of metabolic syndrome, Henriksen et al. [33] performed a longitudinal study which also examined the role of depression as a mediating factor. The findings from this study demonstrated the potential importance of loneliness as a risk factor for metabolic syndrome, further showing that this effect is mediated via depressive symptoms. Accordingly, this study suggested that aiming to reduce loneliness could aid in the prevention of the incidence of metabolic syndrome [33].

Furthermore, Jung & Sikorski [19] explored associations between loneliness and obesity, suggesting that obesity in itself can lead to perceptions of weight stigma and rejection. Indeed, using data from a large representative sample, this study identified that depression, experience of discrimination, and internalised weight bias were associated with higher reports of loneliness [19]. Based on these findings, it is suggested that a greater understanding of the complexity of obesity could help in the elimination of stigmatisation, and, thus, might increase social activities and social networking among this patient group [19].

Another study by Ida et al. [18] sought to investigate factors associated with social isolation and being homebound in older individuals with diabetes. This study identified that insulin use and glycaemic fluctuations were associated with both social isolation and being homebound. Thus, it is suggested that when observing insulin use and glycaemic fluctuations among this patient group, greater attention should be paid to issues in relation to social isolation and being homebound [18]. Furthermore, a study by Brinkhues et al. [34] investigated the association between T2DM and social isolation and the potential elements related to this association. Assessing the relationship between a range of social network characteristics and normal glucose metabolism, pre-diabetes, newly diagnosed diabetes, and previously diagnosed diabetes, this study identified that individuals who were more socially isolated, with smaller social networks, had either newly diagnosed diabetes or previously diagnosed diabetes more frequently, suggesting that this may be an additional useful element to address in the context of T2DM prevention [34].

Similarly important are the data on the effects of loneliness and social isolation on cardiovascular health. Indeed, systematic review and meta-analysis data indicated associations between lack of social relationships and increased risk of coronary heart disease (CHD) and stroke [35]. As these are two leading causes of morbidity and mortality in high income countries, a need is highlighted for prospective studies to examine whether interventions designed to target loneliness and social isolation could prove beneficial to prevent these conditions [35].

Of note, following a comprehensive review of the impact of social isolation and loneliness on cardiovascular and brain health, the American Heart Association (AHA) has recently issued a scientific statement emphasising the need for development and implementation of interventions to enhance cardiovascular health for people experiencing social isolation or loneliness [17]. Although the available data in relation to associations between loneliness, social isolation and heart failure, dementia and cognitive impairment are still limited, this scientific statement highlighted the consistent evidence of the relationship between social isolation, loneliness, and CHD and stroke mortality. Moreover, it further discussed a conceptual framework which suggests that cardiovascular and brain health are affected by social isolation and loneliness via a number of mediating pathways including behavioural (e.g., smoking, diet, and sedentary behaviour), psychological (e.g., depression) and physiological (e.g., inflammatory biomarkers) factors [17]. Whilst acknowledging the limitations of the available literature, which does not suggest causality, this AHA statement concluded that social isolation and loneliness represent under-recognised determinants of cardiovascular and brain health, together with an increased risk of worse health out-

comes among susceptible individuals [17]. Thus, this AHA statement offers a number of suggestions for future research in this field aiming to identify the exact links and mediating mechanisms which may contribute to the effects of social isolation and loneliness on cardiovascular and brain health [17].

On the basis of the above associations and given the close link between NAFLD and other cardio-metabolic conditions, it is probable that loneliness may also be involved in associations between mental health and NAFLD, the detection of which, could help to provide a better understanding of the individual's circumstances and coping strategies against NAFLD.

It is also important to consider further biological factors that might be associated with loneliness, such as circulating stress hormones [14]. Interestingly, the concept of Perceived Desired Social Distance (PDSD) has also been highlighted by Campagne [14], whereby some individuals enjoy being alone, which can in fact be beneficial to health. Indeed, certain programmes aimed at reducing stress, including mindfulness-based programmes, are intended to enhance the value of solitude and being alone [14].

Finally, it should be noted that loneliness is also reported as a predictor of depression, although perceived stress could represent an important mediator between these two variables [64]. Given the negative health impact of depression and psychosocial stress and their association with both a number of NAFLD-related conditions, including obesity, T2DM and CVD [65–67] and loneliness [17,18,34], it is clear that further research should investigate the potential role that these may play in NAFLD and its holistic management.

8. A Compassionate Approach in the Context of NAFLD

The concept of compassion is often described as the sensitivity to the pain or suffering of another, coupled with a deep desire to alleviate that suffering [68]. Compassion applies to a number of situations, equally deserving to play a major role in health care, particularly in the management of chronic conditions, such as NAFLD [69]. Indeed, there has been evidence to suggest that a compassionate approach enhances the management of chronic conditions, helps to relieve anxiety, and can aid a faster recovery from acute illness. Furthermore, studies report that kindness and touch affect the brain function and heart rhythm not only for the recipient, but also for the person providing compassion [70,71]. As reported by Youngson [72], a compassionate approach can also increase pain-tolerance and may alter the brain's response to stress.

Notably, primary care represents the key setting for the management of chronic conditions [73]; however, the outbreak of the COVID-19 pandemic necessitated a number of unforeseen changes in the way in which primary care is delivered. This has led to a deterioration in face-to-face consultations, with such traditional methods being replaced by telephone or video consultations, leading to GP reliance on listening skills rather than encountering the advantages of observation and non-verbal communication [63]. It is probable that in most cases a telephone consultation may suffice, but the lack of the traditional approach in terms of face-to-face communication, may also result in a lack of awareness of unhealthy behaviours, and issues such as weight gain [63].

A compassionate approach is central to the well-being of all individuals, and embracing a compassionate culture within the healthcare system can have positive effects on well-being and stress reduction [74]. This may be even more relevant for complex interventions, such as lifestyle modification and weight management for NAFLD, as there are many factors which may determine the ease at which an individual is able or equipped to successfully make such changes. As such, a compassionate approach may help to better support the individual leading to both physical and psychological advantages, including helping to eliminate feelings of self-blame.

Likewise, as reported by Brenton-Peters et al. [36], the concept of self-compassion—i.e., the tendency or ability to treat oneself kindly in times of failure or distress [36]—may help to support individuals who encounter difficulties in managing their body weight. Of note, systematic review data show that interventions which included aspects of self-

compassion could successfully increase the individual's self-compassion, and that this could lead to positive outcomes in terms of eating behaviours and weight loss [36]. Another systematic review by Austin et al. [37] reported that the feasibility and acceptability of compassion-based interventions among individuals with chronic physical conditions was rated high by participants. Reduced anxiety and depression also emerged from the findings of this systematic review, alongside participants' acceptance of their condition, reductions in feelings of loneliness, and improvements in emotion regulation skills. These findings draw attention to the potential benefits of developing and researching the use of compassion-based interventions for people diagnosed with chronic physical conditions, such as NAFLD [37].

Furthermore, a study by Ralmaho et al. [38] revealed that participants with chronic conditions reported lower levels of self-compassion and compassion from others compared to those without. Moreover, those with a chronic condition also demonstrated higher levels of loneliness and reduced quality of life, whilst compassion was negatively linked to loneliness and positively associated with quality of life within both groups [38]. These findings suggest that a decrease in the ability to be compassionate towards ourselves and a perceived lack of compassion from others can explain reductions in quality of life via increased levels of loneliness [38]. The implications of this study highlight the important role of compassion in loneliness and the need to evaluate potential loneliness in individuals diagnosed with a chronic condition such as NAFLD.

Although the direct evidence/research is lacking, the above may be particularly important in terms of the care of individuals with NAFLD, given the known self-management issues, gaps in NAFLD-related knowledge and information, and the possible risk of perceived loneliness and isolation.

9. Coping Strategies

In addition to the importance of the aforementioned compassionate approach, it is perhaps also crucial to understand the personal circumstances of an individual patient with NAFLD, and to consider the potential value of identifying the utilised personal coping strategies [10]. Particularly for patients with NAFLD, given the implications of the potential fatigue symptomatology and its association with social withdrawal and negative feelings, it is possible that coping strategies might be reduced among this patient population [16].

Overall, a lack of effective coping strategies might interfere with the motivation and management of the condition. Indeed, Hunt et al. [75] suggest that an effective method for achieving weight loss improvement is through the use of motivational interviewing, which represents a collaborative form of communication based on sharing the need for change via an empathetic and supportive approach [75]. This can increase motivation and result in the individual feeling more empowered, thus it has been suggested as an appropriate intervention for NAFLD patients, in order to enhance weight loss through collaboration and a personalized action plan [75].

Moreover, a study designed to investigate the influence of diabetes and obesity on quality of life and coping among patients with NAFLD reported that better quality of life could be predicted by acceptance, active coping and positive framing [39]. The findings from this study further revealed that issues relating to self-blame, denial, and disengagement predicted lower quality of life, and that obesity was associated with enhanced passive/avoidance coping, a further predictor of decreased quality of life [39]. Hence, it is suggested that future interventions for NAFLD should be based on a multidisciplinary approach which should address modification of maladaptive coping strategies [39].

Interestingly, systematic review data regarding the impact of social support on adults with T2DM showed that there is evidence to suggest that positive outcomes in this patient group are influenced by higher levels of social support, suggesting that a greater understanding of the role of social support in the management of diabetes could aid in the achievement of improved diabetes control [76]. Given the significant overlap between T2DM and NAFLD, such data can further inform potential coping strategies for patients

with NAFLD. Indeed, Yasmeen et al. [40] suggest that knowledge regarding the coping strategies utilised by patients with chronic illnesses can help us to better understand the dynamics of such conditions. For example, when studying both cardiac and renal failure patients, significant differences in the coping strategies used by these two groups were identified, with the strategies utilised by the latter being more physical in nature, whereas the former adopted more behavioral and psychological coping strategies [40]. Therefore, understanding the different approaches to coping with the stress induced by chronic disorders is emerging as another important aspect.

Furthermore, although there is limited research regarding the role of prosocial behaviour as a coping strategy to reduce stress, certain studies have adopted this approach. A relevant study, aiming to explore the extent to which prosocial behaviour could buffer the negative effects of stress, showed that such behaviour moderated the effects of stress on positive and negative effect, and mental health overall [41]. Thus, it is suggested that prosocial behaviour could represent an important coping strategy for reducing the impact of stress on emotional well-being, potentially buffering the effect of stress on mental health in a number of ways (e.g., increasing sense of self-efficacy and purpose). Accordingly, prosocial, or helping behaviours could represent a protective factor that may have relevance for broader intervention programmes targeted towards improving coping strategies and overcoming stress in patients with NAFLD.

It is also noteworthy that many people engage in self-rewarding behaviours as a coping strategy to overcome stress, including a tendency to overeat or indulge in other unhealthy options [42]. In this context, another study explored the potential positive effects of prosocial behaviour ('giving to others') as a coping strategy in participants that, following completion of the Trier Social Stress Test, were either sent a gift card for a person chosen by them, or a gift card for themselves [42]. Interestingly, the findings of this study showed that those in the giving group demonstrated greater downregulation of heart rate, diastolic blood pressure, and mean arterial pressure, suggesting that engagement in prosocial behaviour following stress can potentially downregulate the physiological stress response [42].

Finally, a study by Hu et al. [58], which compared non-lonely with lonely people when engaging in empathetic tasks, reported that positive empathy among lonely people appeared to serve as an adpative emotion strategy, resulting in higher perceived social support and effective loneliness reduction. This also contributes to the literature regarding prosocial behaviour and has potential implications for loneliness interventions [58], which could, in turn be exploited for the holistic management of NAFLD.

10. Future Research Directions and Concluding Remarks

NAFLD represents a growing public health issue, with its current management primarily relying on lifestyle modification interventions [11]. Given these parameters, it is plausible that the support needs of individuals with NAFLD—both in primary and specialist care—may often be unintentionally overlooked, enhancing problems, such as loneliness and social isolation, in this patient population. Furthermore, such issues might also emerge from a lack of information/understanding of NAFLD which has been identified as an additional problem in the current routine clinical practice for NAFLD.

This review explored certain aspects relating to NAFLD that extend beyond the routine clinical approach to the management of patients with NAFLD, highlighting possible unmet needs which could place such patients at even greater risk for impaired physical and psychological health. Although limited, and for specific aspects indirect, relevant evidence exists in the scientific literature to suggest important associations between loneliness/isolation and NAFLD and/or NAFLD-associated conditions (e.g., obesity, T2DM, metabolic syndrome, and CVD) [17–20,33,35]. Furthermore, links have been identified between loneliness and psychosocial stress [14,33,45,59], a condition that has also been identified as a risk factor for NAFLD [30–32]. Thus, it is increasingly evident that there are

a number of such features related to NAFLD, which could represent unmet needs among this patient group.

These primarily include a lack of awareness concerning the condition [12,16,21–23] links with chronic fatigue [16,24,48,49]; associations with mental health conditions [10]; and perceived stigmatisation [11,13,15,16,47]. Such factors—each alone and in potentially synergistic combinations–may place individuals with NAFLD at a higher risk of perceived loneliness/isolation and impaired health-related quality of life. Figure 1 presents these factors in a schematic diagram.

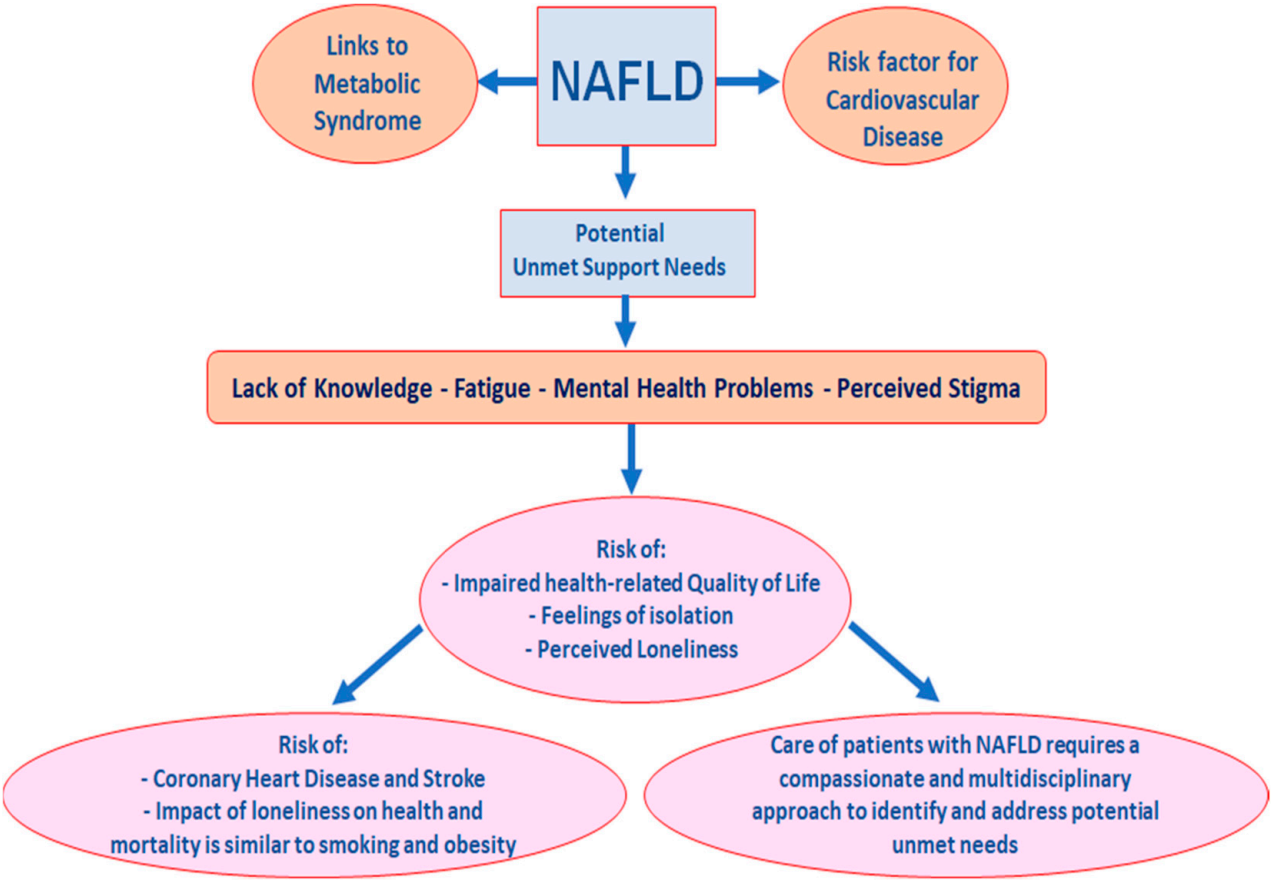

Figure 1. Schematic diagram presenting potential unmet support needs and challenges faced by patients with non-alcoholic fatty liver disease (NAFLD), which could lead to impaired health-related quality of life, together with perceived isolation and loneliness.

Certain limitations should be acknowledged in the context of this review. Indeed, although our search strategy was comprehensive, this could not address the fact that there is a lack of research directly pointing to a link between NAFLD and perceived loneliness/social isolation. Furthermore, whilst we are confident that we have identified the key relevant studies from the available literature, it is probable that there are additional studies indexed on databases other than those searched (PubMed and Google Scholar). However, the objective of this review was not to conduct a systematic review on a specific question of the relevant literature, but to highlight in a broader way, several potential unmet needs of patients with NAFLD, and thus, raise awareness of the possible risks that these issues might pose.

Given the associations between cardiometabolic health, liver disease, and mental health disorders, NAFLD represents a suitable for field for research, education, and training, and also offers an excellent basis for adopting new ways of collaborative working. Indeed, as reported by Karlsen et al., NAFLD highlights the need for collaboration among a range

of specialties including cardiologists, diabetologists, dietitians, hepatologists and general practitioners, together with preventative measures via public health actions [9].

NAFLD is a complex condition with direct and indirect associations with a wide spectrum of other physical and mental health conditions, therefore, a multidisciplinary and compassionate approach is suggested for the holistic management of such patients. This may better address unmet needs of this patient population and aid the individual patient in developing appropriate adaptive coping strategies. To better inform the clinical practice on this holistic approach, further multidisciplinary research is clearly needed to address the multiple gaps in the existing literature.

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