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J. Biomedical Science and Engineering, 2021, Vol. 14, (No. 2), pp: 21-32

Impact of Obesity in Non-Alcoholic Fatty Liver Disease

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Keywords: Non-Alcoholic Fatty Liver Disease, Obesity, Diabetes, Cardiovascular Diseases, Insulin Resistance Metabolic Syndrome and Biopsy

Received: April 4, 2019 **Accepted:** February 1, 2021 **Published:** February 4, 2021

ABSTRACT

"Non-alcoholic fatty liver disease" is the alarming health risk around the world today. Nearly 1/3 of the world's population is affected by non-alcoholic fatty liver disease. Many scientists put forward two hit hypotheses to explain the pathophysiology of non-alcoholic fatty liver disease. With the aid of trials using Biopsy, ultrasound scan and molecular techniques, scientists explained an authentic evidence of non-alcoholic fatty liver disease progression is ultimately because of obesity and its commodities, such as Cardio vascular diseases, Diabetes and Metabolic syndrome. This review mainly focuses on how obesity leads to non-alcoholic fatty liver disease based on statistical analysis of different research studies conducted by the research scientists. In the analysis of 1980-2003, out of 505 individuals, 305 were affected with NAFLD and among them, 64.3% were obese. In the analysis of the period of 1996-2002, out of 550 NAFLD patients, 70.36% were obese. Also in the analysis of 2010-2015 period of time, mostly 90% of the NAFLD patients were obese. It was also revealed that, along with NAFLD and obesity, diabetes and hyperlipidemia also exist as the commodities of obesity. Attention of medical field is towards the treatment and analysis of non-alcoholic fatty liver disease which is expected to be the reason of liver transplant by 2020.

1. INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) is a hallmark of steatosis and a major challenge for liver abnormalities and gastroenterology today [1-3]. In 1980, NAFLD was introduced to the world for the very first time by Ludwig and his colleagues. In literature, NAFLD plays a vital role in morbidity and mortality along with no signs and symptoms [4]. It encompasses with 4 stages beginning with simple steatosis (see **Table 1**).

It was estimated that in the general population, 10% to 30% are affected by NAFLD. The clinical investigations of NAFLD always depend on natural history and prevalence worldwide. Subsequently, several researches highlight that basic reason for NAFLD is obesity [5].

Table 1. **Stages of non-alcoholic fatty liver disease.**

Stages	Description	Reference
1) Simple steatosis	Harmless accumulation of fats in hepatocytes	[4-6]
2) Non-alcoholic steatohepatitis (NASH)	The liver becomes inflamed because of more and more fat accumulation	[4, 7, 8]
3) Liver fibrosis	Formation of scar tissue around the inflamed hepatic tissues and nearby blood vessels	[4, 9, 10]
4) Liver cirrhosis	Final stage of NAFLD this severe stage occurs after many years of inflammation finally leading to liver failure. Permanent damage to liver.	[4, 11, 12, 13]

Also, Obesity is considered as the gateway for other comorbidities such as malignancies, cardio vascular diseases (CVD), metabolic syndrome (MS), diabetes mellitus (DM), hypertension and insulin resistance (IR) which were the main risk factors for the progression of the condition called NAFLD [14-17].

2. OBESITY

Obesity has become a pandemic concern along with its rapidly progressing prevalence around the world [18]. Obesity is the increased Body Mass Index (BMI). BMI threshold values are used worldwide to categorize individuals in to different groups as shown in **Table 2**.

BMI reflects excess fat accumulation around the body [19]. In United States, for obesity the BMI cutoff value is defined as 30 Kg/M^2. It may vary depending on race and phenotypic classifications [20]. According to WHO, Obesity has risen intensely affecting both children and adult. 1/3 of the population is obese. Among them 39% are adults, 41 million are children. This clearly illustrates the progression of obesity around the world [18].

3. TWO HIT HYPOTHESES

Overall scientific literature shows cases, that the origin of NAFLD is multifactorial [21]. Though the pathology of NAFLD is still unknown, according to many research articles its pathology is defined by two hit hypotheses [11, 22, 23]. According to Croke and Sampson (2012), the first hit hypothesis is due to Metabolic syndrome, Insulin resistance and later on to CVD. This leads to the surge in the levels of free fatty acids in liver [24]. The surge, causes the impairment of filtration of fatty acids in liver eventually leads to apoptosis, steatosis and NAFLD [25].

Since one hypothesis is not enough to conclude the pathophysiology of NAFLD, Maheshwari and Thuluvath (2006), states that the first hit hypothesis and its impact on liver leads to many factors such as oxidative stress, diabetes, mitochondrial dysfunction and inflammatory cytokine reactions that defines the second hit hypothesis [26].

4. RISK FACTORS OF NAFLD UNDERLINED OBESITY

Subsequently several researches have stated that these hypotheses which highlights IR, DM, inflammatory cytokines and fatty acid accumulation in liver ultimately from obesity and the correlation with these factors and NAFLD [9, 23, 27].

According to Charlton *et al* (2011) NASH and NAFLD are acknowledged as the main attestation for liver transplantation and also will be anticipated as the governing cause of liver transplantation by 2020.

Table 2. WHO classification of BMI and obesity [19].

Classification	BMI (kg/m^2)	
Underweight	<18.50	<18.50
Severe thinness	<16.00	<16.00
Moderate thinness	16.00 - 16.99	16.00 - 16.99
Mild thinness	17.00 - 18.49	17.00 - 18.49
Normal range	18.50 - 24.99	18.50 - 22.99
		23.00 - 24.99
Overweight	≥25.00	≥25.00
Pre-obese	25.00 - 29.99	25.00 - 27.49
		27.50 - 29.99
Obese	≥30.00	≥30.00

American journal of gastroenterology reported along with the investigations of majority of population through ultrasound scan testing, it was revealed that NAFLD is progressing worldwide because of obesity and its comorbidities such as metabolic syndrome, diabetes mellitus, insulin resistance and cardio vascular diseases [20, 28].

"National health and nutrition examination survey" which was conducted in 1988-1994, also emphasized that 1/3 of the population were subjected with NAFLD and among them 90% of subjects were obese [29]. Major risk factor of NAFLD is obesity and this obesity is due to the contribution of multiple factors such as genetic background, lifestyle, food patterns and environmental factors as well [11, 22]. To analyze the impact of obesity in NAFLD since the concomitance of obesity with IR, metabolic syndrome, T2DM, and inflammatory cytokines, many research articles were based on imaging, laboratory and histological findings. While the patients were ruled out of consuming alcohol or other drugs [30].

Obesity due to excess visceral adiposity along with lectin which is a product and responsible gene of obesity, involves in a dramatic role in modulation of insulin sensitivity whereas leading to insulin resistance and T2DM [1, 31].

Studies also support that obesity and high calorie intake leads to hepatic insulin resistance. This excess accumulation of fatty acids leads to chronic inflammation around the outlying adipose tissues, which directs to metabolic syndrome and surge in "inflammatory cytokines" such as TNF-alpha, IL-8, IL-6, CRP, MCP and some decreased levels of "anti-inflammatory adipokines" such as IL-10 and adiponectin leading to insulin resistance [31].

Odegaard and Chawla (2008), via testing bacteria and parasite about the innate immune modulation in obesity also supports that this surge in the levels of inflammatory cytokines and decreased levels of anti-inflammatory adipokines is the natural phenomenon in the development of insulin resistance (IR) and gradually to diabetes mellitus (DM).

Fatty acid accumulation in liver underlined obesity also promotes peroxisomal and mitochondrial β-oxidation which enhances microsomal induction of both CYP2E1 and CYP4A1 [31]. Also in the consecutive year [32] sates that this microsomal induction leads to the increased reactive oxygen species in liver promoting mitochondrial dysfunction, steatohepatitis and eventually to NAFLD. According to a study by [33], the mortality in NAFLD patients was due to CVD and malignancy. This study also states that these people were exposed to an obesity risk factor that progressed towards developing T2DM as well.

Table 3 below shows the demographic details of patients with NAFLD around 1980-2003. These studies states that NAFLD is more frequent in females, these studies also showcase with higher prevalence of obesity and the frequent prevalence of T2DM respectively.

Table 3. Trials of NAFLD and risk factors obesity and diabetics.

Journal Author	Number of patients with NFLD	Percentage of female with NAFLD	Percentage of obesity	Percentage of Diabetes
[34]	20	65%	90%	25%
[4]	49	78%	69%	51%
[12]	42	83%	93%	36%
[35]	90	51%	87%	46%
[36]	104	17%	25%	7%

The above statistical analysis illustrates a clear picture that, among 505 individuals in the study, 305 were affected with NAFLD. Obesity is in its peak around 64.3% and diabetes around 21% but in those studies, it was also mentioned, there were individuals who developed diabetes as the ultimate reason of obesity [36]. Evidences also show that individuals who were diabetic also developed NAFLD later [4].

A study conducted by Blackett and Sanghera (2016) states that NAFLD is strongly linked with obesity resulting in metabolic syndrome, diabetes and CVD. These trials also emphasize mortality rates of NAFLD are due to developed CVD as a risk factor. It also states that NAFLD is strongly linked with obesity resulting in metabolic syndrome, diabetes and cardio vascular diseases. These trials also emphasize mortality rates of NAFLD patients, due to CVD was high which was also a risk factor of NAFLD [37] (**Table 4**).

There are so many trials which were tested to analyze the impact of obesity in non-alcoholic fatty liver disease since it also creates so many risk factors such as diabetes and, metabolic syndrome due to hyperlipidemia. As shown in **Table 5** below, almost in all trials the above said risk factors were observed simultaneously which gave a clear picture that NAFLD was the ultimate cause of obesity. Since obesity was elicited in a higher percentage of the populations tested [1, 22].

5. VALUATION OF NAFLD AROUND THE WORLD

Statistically 30% of the general population in the world was affected by NAFLD [4, 47]. Numerous investigations have revealed the possible association of NAFLD for higher rates of mortality today. Nevertheless, obesity underlined risk factors such as CVD, IR, metabolic syndrome, inflammation and hepatic carcinoma, increases the progression of NAFLD [22, 31].

According to WHO calorie intake and obesity seemed to be double from1980. Rafiq and his colleagues (2009) also state that 39% of NAFLD adult patients around the world were obese. Rinella and Charlton (2016) emphasizes that USA was in the center position of Obesity and NAFLD [21, 31].

5.1. USA and NAFLD

Younossi and his colleagues (2016) analyzed 70 reports published around 1989-2015 consisted with a specific sample size (8,515,431) from 22 different countries which emphasizes that 28.65% - 30% of population around the world were affected by NAFLD and with a higher prevalence in USA along with increased obesity [29].

A cohort study states that prevalence of NAFLD at USA was increased by a factorial of 2.8 within the period of 9 years (2003-2011). This also mentioned NAFLD will continue to be a major risk along with increased rate of obesity [49].

A biopsy study and constant monitoring in 20 obese patients suspected of NAFLD within the period of 1985-2001, along with ethnic diversities such as Caucasians-59%, Hispanics-36%, African American 5%. Among the individuals 64% were with hyperlipidemia and 41% were with diabetes. This study highlighted that all individuals were affected with NAFLD and the biopsy images revealed the fibrous liver in the last year of examination [50].

Table 4. Some trials of NAFLD underlined Obesity with the risk of CVD.

Year	Method	Population (n)	Findings	Reference
2010	MRI evaluation	n = 66, American pediatric population	100% obese Along with high VLDL concentration and increased CVD risks	[38]
2010	Liver biopsy	n = 118, Swedish NAFLD patients	Increased morality of NAFLD patients due to CVD 90% are obese	[39]
2013	Liver biopsy MRS Endocardiography	Adults population based study	At MRI n = 54 with obese and intrahepatic try glyceride was high, worse systolic and diastolic functions	[31]
2012	Endo cardiograph, and ultra sound scan test	n = 165	N = 97 were obese and showed elevated levels of amino transferases along with systolic and diastolic dysfunction	[40]
2015	Systemic literature search	12 studies, 9 were adults' population based and 3 were pediatric studies	Children and adults were obese and had NAFLD along with CVD	[41]

Table 5. Trials of NAFLD underlined obesity and its risk factors.

Reference	Year	Number of NAFLD Patients	Diabetes (%)	Obesity (%)	Hyper lipidemia (%)
[42]	1996	40	36	70	38
[43]	1999	134	38	70	32
[44]	1999	144	18	60	37
[16]	1999	30	43	80	13
[35]	2001	90	46	87	61
[45]	2002	66	35	67	82
[46]	**2002**	46	34	72	34

Trials based on the impact of obesity in NAFLD individuals around 2005 showed a clear-cut evidence. ALT level analysis of 4376 individuals revealed 41.1% were obese and among the obese 7% were affected by NAFLD [51]. CT scan analysis of n = 742 population based study elicited 68.6% were affected with NAFLD and among those individuals 39.1% were obese [52].

A study conducted by Laurin and his colleagues (1996) at USA along with 2287 obese patients' states that, prevalence of NAFLD varied according to ethnicity. Whereas 45% of them are Hispanics, 24% were

blacks and 33% were whites. Nevertheless, this study has a profound impact on NAFLD underlined obesity [42].

Data obtained in America within the period of 1999-2002 and 2009-2012 were analyzed by "National health and nutrition examination survey" on NAFLD underlined fibrosis and obesity [20]. This survey elicits a significant increase in diabetes, IR and obesity as well. All the data were under the p value of 0.005. The percentages of the above-mentioned risk factors were given below [19].

Among American adults from 1999-2002 obesity was 29.8% which turned significantly high around 2009-2012 as 36.6%. Whereas percentage of diabetes from 1999-2002 was 8.3% which also showed the rate of elevation up to 11.9% around 2009-2012 [19]. Also from 1999-2002 insulin resistance was 34.7% which was also elevated up to 42.1% in 2009-2012 periods of study. This clearly gives an overview of the progression of NAFLD ultimately because of the higher rate of obesity prevailing in USA [19, 39, 51, 53].

At present obesity and diabetes were the alarming risk factors of the progression of NAFLD in USA. Some of the trials emphasizes that there was a difference in the progression of NAFLD based on ethnicity as well [54].

As shown in **Figure 1**, the statistical data shows 60% - 76% of NASH and 22% of NAFLD could be observed in diabetic patients in USA. T2DM also prevailing as the independent risk factor for NAFLD, NASH and hepatic carcinoma which reflects high calorie intake or obesity in USA [28].

The survey of "International Diabetic Federation" illustrates 10.7% of the adults were affected by diabetes and NAFLD in Caribbean islands and Northern America. Also, it emphasizes obesity leads to T2DM and to metabolic syndrome which noticed in 20% - 80% of NAFLD, diabetic and along with obese patients [14]. Ethnicity also plays as a predictor of NAFLD. Many trials in America prove that there is a difference in progression of NAFLD based on ethnicity. Statistics also illustrates among Americans, Hispanics shows the higher rate of NAFLD [55]. Adult population based study of 1,026 individuals also highlights that Hispanics were highly affected than the African American or other ethnic diversities in USA [56].

Almost all trials in USA concludes that based on the rate of obesity, NAFLD rates estimated to be 29% in USA, 28% in Belize, 28% in Barbados, 28% in Mexico, 24% in Venezuela and 20% in Uruguay [14, 55, 57].

5.2. Impact of Obesity around UK, China, Italy and Srilanka

A biopsy study of 108 NAFLD patients in UK for about 6 years showed 42% with severe NAFLD, 40% were stable with initial NAFLD and 18% were with progression of severe fibrosis [57]. A meta-analysis of a pediatric study at UK, show cases that most of the children were obese and showed the elevation of transaminase levels in their blood samples collected. The levels are to be more than 40UL and around 41% - 89%, which elicits the prevalence of NAFLD along with Obesity [3, 32].

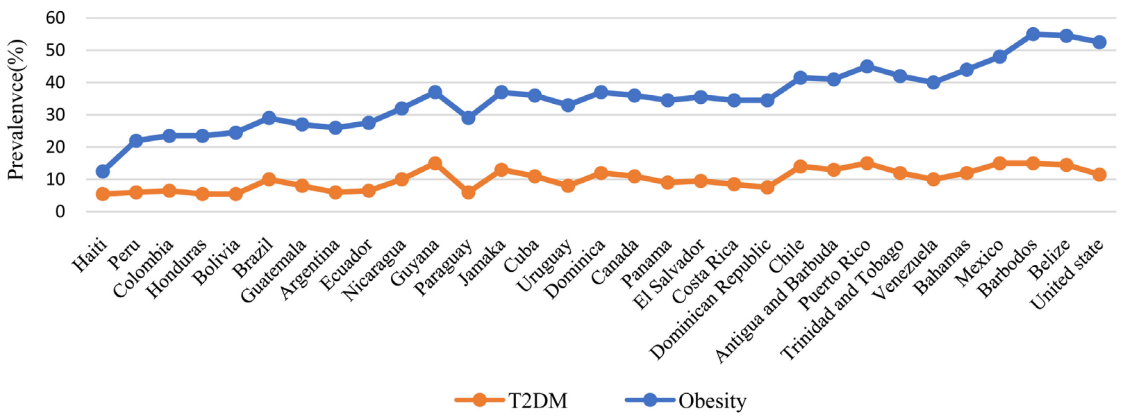

Figure 1. Illustrate the prevelence of T2DM and obesity around America [14, 48, 55].

A study conducted in Italy with randomly selected 992 individuals were examined with ultrasound scan, parameters of amino transferases and also physical examination elicits 412 individuals (41.5%) were obese. Among this study population 24.8% were presented with NAFLD, 34.4% with metabolic syndrome and 34.4% were presented with diabetes. It was also emphasized that these individuals affected with NAFLD and obesity were in the higher risk of developing cardio vascular diseases. Since the study population had 34.7% hypertension and 34.2% with hyperlipidemia [31].

Interestingly a study conducted at china based on women suspected to develop NAFLD after post menopause. 4218 post-menopausal women were selected for this trial. Among the study population it was revealed that 32.5% (n = 1370) were affected with NAFLD. Overweight and obesity was noticed as 54.2% and 49.8% respectively. Insulin resistance in these individuals were noticed round 27.7% which gave an evidence that post-menopausal women also have the higher risks of developing NAFLD underlined obesity and its commodities as well [30].

Developing countries also now analyze the NAFLD and its prevalence which is asymptomatic in many individuals. An adult study population of 3012 participants was selected for a trial at Srilanka with the collaboration of "International Center of Japan" (IMCJ). This study population consisted with different ethnic diversities of Sinhalese (34.9%), Tamils (30.6%) and Muslims (33.3%). NAFLD was observed in 31.6% of men and 37.5% of women among the study population. Further investigations revealed 70.3% were obese [58].

6. ONGOING STUDIES RELATED TO NAFLD

Ongoing studies are focused on the genetic background of NAFLD. Some trials also emphasize that progression of NAFLD is due to variation in PNPLA3 gene which was responsible for breakdown of fats in liver. Due to this variation of PNPLA3 gene it leads to increased production of PNPLA3 and decreased fat breakdown eventually leading to fat accumulation in liver and obesity. Alteration of HIPK 3, AQP9 and TNNI3 also leads to obesity. However, this whole mechanism was not fully understood and the research is still ongoing [30].

7. TREATMENT

In treatment of NAFLD the first line was always based on lifestyle modifications which include exercise and dietary modifications which help the patient to lose weight. It was stated that if the patient reduces the weight by 5% it showed much improvement in the damaged liver due to NAFLD [59, 60]. Treatment strategies also focused on central appetite suppressants such as Rimonabant, which was an antagonist of cannaboid receptor [61]. Measures are also taken to slow the absorption, drug therapies for insulin resistance, hyper cholesterol levels and diabetes mellitus as well. Different types of bariatric surgeries are also done in patients with NAFLD [48].

Scientists are working on the future development of NAFLD therapy that mainly focus on insulin sensitizing agents that could target PPAR agonists which also reduces the risk of diabetes, bile acid metabolism to reduce the fat accumulation in the liver, induce fat breakdown and filtration of fats in liver. Scientists also focus on anti-inflammatory drugs and anti-fibrotic drugs which could reduce the rate of formation of fibrosis mechanism in liver [28]. Fascinatingly some of the studies also revealed that caffeine in coffee could decrease the rate of liver damage and fibrin formation in hepatocytes [49].

8. SUMMARY

This review analyzed the relationship between obesity and NAFLD. From the trials briefed in this review, it is clearer that NAFLD's ultimate reason is obesity. Obesity leads to insulin resistance, metabolic syndrome, diabetes, cardio vascular diseases and malignancies which were the major risk factors of NAFLD. This review also emphasizes that 1/3 of the world's population was affected by NAFLD which is asymptomatic. Pathophysiology of the condition of NAFLD could be explained by two hit hypotheses.

Literature and statistics elicits majority of the NAFLD patients were obese, who later develops its commodities as diabetes and cardiovascular diseases. Statistics also states that NAFLD will be the major reason for liver transplantation in future world. It also states that NAFLD will be the ultimate reason for the hepatic carcinoma by 2020. Moreover, according to the statistical analysis of this review, it shows cases that majority of pediatric population around the world is affected by obesity because of the consumption of junk foods and soft drinks, which leads them to develop NAFLD and comorbidities of obesity. Since treatment and diagnosis were available for NAFLD, much attention should be given to reduce the rate of progression of NAFLD which is a major health risk hidden in the population today.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest regarding the publication of this paper.

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