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Prevalence of microvascular complications in patients with NAFLD

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ABSTRACT

Background: Non-alcoholic fatty liver disease (NAFLD) is a common liver disorder that is strongly associated with Type 2 Diabetes Mellitus (T2DM).

Objective: This study was designed to determine the prevalence of NAFLD among T2DM patients and to evaluate whether there is an association between NAFLD and diabetic microvascular complications.

Methods: This was a hospital-based cross-sectional descriptive study conducted during one year from January 2018 to December 2018. A total of 107 type 2 diabetes patients were submitted to clinical and laboratory evaluation and abdominal ultrasonography for NAFLD detection. Statistical analysis such as the chi-square test, and univariate and multivariate logistic regression was used in this study.

Results: Out of 107 type 2 diabetic patients, 54.2% patients had NAFLD whereas 45.8% had no fatty liver on ultrasonography. NAFLD group had a significantly higher prevalence of retinopathy (41.4% versus 20.4%, P-value 0.02), neuropathy (58.6% versus 14.3%, P-value <0.001), and nephropathy (67.2% versus 49.0%, P-value <0.05). Moreover, after logistic regression was done, diabetes patients with NAFLD had 8.88 times the risk of neuropathy than those without NAFLD (OR= 8.88 95% CI: 2.95-26.74, P-value <0.001).

Conclusion: The prevalence of NAFLD is higher in type 2 diabetes patients. This study also reported the prevalence of microvascular complications was higher in patients with NAFLD. Therefore, ultrasound examination of the liver for NAFLD can be used as an early marker of diabetes and its complications.

Keywords: Microvascular complications, Non-alcoholic fatty liver disease, Type 2 diabetes patients

1. Introduction

Diabetes mellitus represents one of the most significant non-communicable diseases, with its prevalence steadily increasing worldwide. Among the different types, Type 2 Diabetes Mellitus (T2DM) predominates, accounting for approximately 90% of all diabetes cases [1]. The global prevalence of diabetes was estimated at 2.8% in 2000 and is projected to rise to 4.4% by 2030, with the total number of cases expected to escalate from 171 million in 2000 to 366 million by 2030 [2]. Notably, diabetes mellitus is more prevalent in men than in women.

Myanmar, such as many other developing countries, is experiencing a double burden of diseases due to demographic and socio-economic transitions. The government has seen a significant rise in the prevalence of diabetes mellitus, with WHO estimates indicating an increase from 2.4% in 1995 to a projected 3.2% by 2025. Data from the STEPS survey in 2014 revealed that the overall prevalence of adult-onset diabetes in Myanmar was 10.5% [3], with urban areas such as Yangon showing particularly high rates.

Alongside the rise in diabetes, Non-Alcoholic Fatty Liver Disease (NAFLD) has emerged as a common cause of chronic liver disease globally, particularly in individuals with obesity and T2DM [4]. Since its initial identification in the 1980s, NAFLD has been recognized as a major complication of T2DM, with studies highlighting the increasing prevalence of this condition in Asian countries, including Myanmar.

NAFLD is closely linked with microvascular complications in patients with T2DM) through shared metabolic pathways. Central to this relationship is insulin resistance, a common factor in both conditions, which disrupts glucose and lipid metabolism. This leads to excess fat storage in the liver, promoting inflammation and oxidative stress. These processes impair endothelial function and heighten the risk for microvascular complications such as retinopathy, nephropathy, and neuropathy. Studies also suggested that NAFLD may exacerbate the progression of these complications independently of traditional cardiovascular risk factors, emphasizing the importance of early detection and management of NAFLD in diabetic patients to mitigate these risks [5, 6].

Despite the recognized association between NAFLD and diabetes mellitus, there is a paucity of studies specifically examining the prevalence and clinical implications of

NAFLD in diabetic populations, particularly in Myanmar. This study aimed to investigate the prevalence of NAFLD among patients with T2DM and exploring the association between NAFLD and microvascular complications in this population.

2. Methods

2.1 Study area

This study was carried out on Diabetes Outpatient clinic and medical units, the Department of Radiology and the Department of Diabetes and Endocrinology at North Okkalapa general and teaching hospital**.**

2.2 Study design

This study was hospital based cross-sectional analytical study.

2.3 Sample size and sampling

The prevalence of fatty livers in patients with type 2 diabetes mellitus was 56.6% (Somalwar et al, 2014). The minimal sample size (n) was calculated using the following formula with 95% confidence interval and 95% power of the test. Added non-response rate was considered 10%; therefore, the sample size was 105 patients.

2.4 Data collection

A cross-sectional study was conducted among the patients with type 2 DM according to exclusion and inclusion criteria. The patients were selected by the convenient sampling. After doing the simple random selection, patients with type 2 diabetes who gave informed consent were included in the study. Personal details of the patient were recorded. Detailed medical history and clinical examination of the patient was done (including the measurement of Body Mass Index (BMI) and waist circumference). 10 ml of venous blood was drawn from each volunteer in this study using a disposable plastic syringe to do laboratory investigation including Glycosylated hemoglobin (HbA1c), and serum creatinine level. Serology for viral hepatitis B and C was also assessed in all participants. Urine RE and Urinary Albumin-Creatinine ratio (UACR) for detection of proteinuria was done. Ultrasonography examination of abdomen was carried out at the radiology department of North Okkalapa General Hospital to determine the size, echogenicity of liver and the presence of non-alcoholic fatty liver. Diabetic Retinopathy (DR) was assessed by retinal photograph, which was confirmed by an experienced physician or an ophthalmologist. Diabetes nephropathy was assessed by finding evidence of kidney injury

by UACR and calculating eGFR from creatinine result. Diabetes neuropathy was assessed by using Michigan Neuropathy Screening Instrument. The results were recorded in the proforma form. The various laboratories, clinical variables, presence of retinopathy, nephropathy and neuropathy were compared in study groups.

2.5 Data analysis

Data collection was done using a proforma. To ensure completeness, consistency, and correctness, the data were manually recorded by the interviewers. After checking the data and code, data entry was done in Epi-data software version 3.02. For data validation, a checked file was used, and data was edited if necessary. Data analysis was performed by using SPSS package version 16. For descriptive data, frequency distribution and cross tables were constructed. Chi-square and regression were used to find the association between non-alcoholic fatty liver disease and microvascular complications in patients with type 2 diabetes mellitus. The significance of level was remarked at a P-value 0.05.

2.6 Ethical clearance

The research protocol was submitted to the Academic Board and Ethical Review Committee of University of Medicine 2, Yangon and it was carried out only after getting approval of Ethical Review Committee. This study obtained ethical approval from the institutional research ethics review committee, the University of Medicine (2), Yangon, Myanmar in February 2020 [Reference no. Ethical (248/2017)].

3. Results

Out of 107 patients with T2DM, 58 (54.2%) were found to have NAFLD (Table 1). The age distribution among the patients revealed that 45% of those under 50 years of age had NAFLD, compared to 58% of those over 50 years. However, the age difference between the NAFLD and non-NAFLD groups was not statistically significant (P-value = 0.225). Gender distribution was also examined, with the results showing that 58% of male patients had NAFLD compared to 53% of female patients. Despite this difference, the gender distribution between the NAFLD and non-NAFLD groups was not statistically significant (P-value = 0.645). Glycaemic control, measured by HbA1c levels, was another key factor explored in the study (Table 1).

Table 1: Proportion of NAFLD in study population (n=107)

Description	Number	Percentage
With NAFLD	58	54.2
Without NAFLD	49	45.8
Total	107	100.0

Among patients with HbA1c levels above 7%, 55.4% had NAFLD, whereas 44.7% of those with HbA1c levels below 7% had the condition. Despite this variation, the difference in glycaemic control between the two groups was not statistically significant (P-value = 0.417). One of the most significant findings of the study was the relationship between the duration of diabetes and the presence of NAFLD. Among patients with a diabetes duration of less than 10 years, 47.1% had NAFLD, while a striking 81.8% of those with a duration of more than 10 years were affected. This difference was statistically significant (P-value = 0.002). The study also focused on the prevalence of microvascular complications among T2DM patients with and without NAFLD. Retinopathy, nephropathy, and neuropathy were more common in patients with NAFLD. Specifically, 41.4% of patients with NAFLD had retinopathy, compared to 20.4% without NAFLD. Similarly, 67.2% of patients with NAFLD had nephropathy, versus 49% without NAFLD. Neuropathy showed the most significant association, with 58.6% of NAFLD patients affected, compared to just 14.3% of those without NAFLD. The strong link between NAFLD and neuropathy was statistically significant (P-value < 0.001), with NAFLD patients being nearly nine times more likely to develop neuropathy (Table 2).

Table 2: Association with microvascular complications between patients with or without NAFLD in study population (n=107)

Characteristics	With NAFLD (n = 58)		Without NAFLD (n=49)	
	Number	Percentage	Number	Percentage
Age				
≤ 50 years	15	45	18	55
> 50 years	43	58	31	42
Sex				
Male	14	58	10	42
Female	44	53	39	47
Duration of Diabetes Mellitus*				
≤ 10 years	40	47.1	45	52.9
> 10 years	18	81.8	4	18.2
HbA1c				
≥ 7%	51	55.4	41	44.6
< 7%	7	44.7	8	55.3
Retinopathy*				
Present	24	70.6	10	29.4

Characteristics	With NAFLD (n = 58)		Without NAFLD (n=49)	
	Number	Percentage	Number	Percentage
Absent	34	46.6	39	53.4
Neuropathy**				
Present	34	77.4	7	22.6
Absent	24	36.4	42	63.6
Nephropathy*				
Present	39	61.9	24	38.1
Absent	19	43.2	25	56.8

* P-value <0.05, ** <0.001

Univariate Binary logistic regression showed that patients with NAFLD had increased risk of 8.88 times of neuropathy than those without NAFLD [OR 8.88, 95% CI: 2.95 - 26.74, P-value <0.001]. When other complications were studied separately, the frequency of retinopathy and nephropathy were not as much significant as neuropathy in the association with non-alcoholic fatty liver disease (Figure 1).

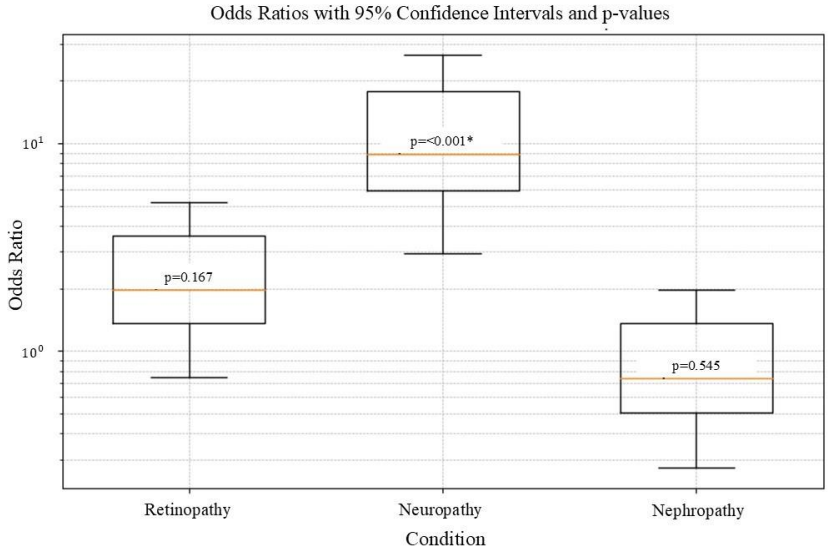

Figure 1: Association with microvascular complications between patients with or without NAFLD in study population (n=107)

4. Discussion

Non-alcoholic fatty liver disease (NAFLD) is increasingly recognized as a common comorbidity in patients with Type 2 Diabetes Mellitus (T2DM), closely linked to insulin resistance and various diabetic complications. The mechanisms linking NAFLD to microvascular complications in T2DM are thought to involve several interconnected pathways, including insulin resistance, chronic inflammation, oxidative

stress, and endothelial dysfunction. Insulin resistance, a central feature of both T2DM and NAFLD, leads to lipid accumulation in the liver and triggers a cascade of metabolic disturbances that contribute to systemic inflammation. This inflammation results in the release of pro-inflammatory cytokines (such as TNF-α and IL-6), which not only damage liver tissue but also impair vascular endothelium, a key factor in microvascular complications like retinopathy, nephropathy, and neuropathy. Additionally, oxidative stress from hepatic lipid metabolism generates reactive oxygen species (ROS), which further harm endothelial cells, compromising blood flow and vascular integrity. Endothelial dysfunction, fuelled by reduced nitric oxide bioavailability, exacerbates vascular stiffness and disrupts microcirculation. This cumulative effect of inflammation, oxidative stress, and endothelial impairment establishes a pathogenic link between NAFLD and the progression of diabetic microvascular complications [5-7].

In this study, 107 patients, including both inpatients and outpatients, from North Okkalapa General and Teaching Hospital in Yangon, Myanmar, were assessed for the presence of NAFLD. The results revealed that 58 patients (54.2%) had NAFLD, as detected by ultrasonography, while 49 patients (45.8%) showed no signs of fatty liver. This prevalence is higher than that reported in a previous study by *Myat Thu et al.* conducted at New Yangon General Hospital and Yangon General Hospital, where 43% of 70 diabetic patients were found to have NAFLD [8]. The increase in NAFLD prevalence among the diabetic population in Myanmar suggested a growing burden of these diseases over time.

Comparative studies from other countries also underscored the significant prevalence of NAFLD in T2DM patients. For instance, *Wen-Shan et al*. (2013) in China reported that approximately 61% of 1,217 inpatients with T2DM had NAFLD [9]. Similarly, *Suresh et al. (2014)* in India found a 35% prevalence of fatty liver among 141 diabetic patients [10], while *Somalwar et al. (2014)* noted that 68 out of 120 T2DM patients (56.66%) had fatty liver, as confirmed by ultrasonography [11]. These studies used ultrasound as the diagnostic tool, and the prevalence rates reported are comparable, reinforcing the consistency of NAFLD prevalence across different diabetic populations.

The current study found that the mean age of patients with and without NAFLD was

similar, with NAFLD patients averaging 57.6 ± 10 years and non-NAFLD patients 55.67 ± 12.19 years. The overall average age was 56.72 ± 11.1 years, with a range from 28 to 86 years. Gender distribution showed that 24 patients (22.4%) were male, while 83 patients (77.6%) were female. These findings are not entirely consistent with previous research. *Targher et al. (2007)* observed that NAFLD prevalence increased with age, particularly among those aged 40-59 years (65.4%) and those aged 60 years and above (74.6%, P <0.001) [12]. On the other hand, *Williamson et al.* reported that participants with definite steatosis were significantly younger and had a shorter duration of diabetes than those in the normal or probably normal groups [13].

Wen-Shan et al. (2013) also reported age-related differences in NAFLD prevalence, noting a significant decrease in prevalence with increasing age (9). In their study, NAFLD was more prevalent in men than in women (74.5% vs. 72.3%, P > 0.05) among those under 50 years of age. However, this trend reversed in the older age groups, with women having higher prevalence rates in both the 50-60 years group and those over 60 years. These findings suggested that the relationship between age, sex, and NAFLD prevalence is complex and may vary by population, showing the need for further research to clarify these associations.

In this study, the mean HbA1c level among patients with NAFLD was 9.4 ± 2.37, compared to 9.01 ± 2.56 in patients without NAFLD. This difference was not statistically significant (P = 0.417), indicating that glycaemic control, as measured by HbA1c, may not be a peculiar factor between those with and without NAFLD. These findings contrast with those of *Somalwar et al. (2014)*, who reported higher HbA1c levels in patients with NAFLD compared to those without [11].

However, the duration of diabetes was found to be significantly longer in patients with NAFLD. This is consistent with *Somelwar et al.*'s findings, which indicated that the prevalence of NAFLD increases significantly with the duration of diabetes [11]. Conversely, *Wen-Shan et al. (2013)* reported a significant decrease in NAFLD prevalence with longer diabetes duration, highlighting potential differences in disease progression and NAFLD development across populations [9].

Moreover, it is essential to highlight that NAFLD has been independently associated with a higher prevalence and severity of these complications among individuals with

T2DM. Studies have shown that patients with T2DM and NAFLD are at an elevated risk for complications like diabetic nephropathy, retinopathy, and neuropathy compared to diabetic patients without NAFLD. This association is likely due to overlapping metabolic disruptions, such as insulin resistance and chronic inflammation, that are characteristic of both NAFLD and diabetes [5, 6]. Additionally, NAFLD may aggravate insulin resistance further, leading to worse glycaemic control and indirectly promoting the progression of these microvascular complications [7, 14, 15].

Some journals reported that diagnosis of diabetic retinopathy and diabetic nephropathy was inversely associated with the presence of NAFLD. *Wen-Shan et al., (2013)* also reported the prevalence of NAFLD in patients presenting with diabetes nephropathy, neuropathy and retinopathy was 49.4%, 57.2% and 54.9%, respectively and rates were significantly lower than those of patients without diabetes nephropathy, neuropathy and retinopathy (65.9%, 65.6% and 66.1%, respectively) [9]. The above two findings did not seem to be consistent with other research and the present research. This might be due to diversity of studied patient's ethnicity and racial differences.

Reviewing various kinds of research on association of NAFLD and microvascular complications, it is difficult to achieve a common finding regarding the scope of fatty liver as an independent risk factor for various microvascular complications of diabetes. Therefore, large scale randomized studies with wide discussions from endocrinologists, nephrologists, neurologists, gastroenterologists, physicians and ophthalmologists will be more needed for the better appreciation of this issue.

The strength of this study is the exact ultrasound by single expert operator and relatively sufficient sample size to assess the prevalence of NAFLD in patients with T2DM. A limitation was that the diagnosis of NAFLD was based on ultrasound imaging. The patients did not undergo liver biopsy and histological examination, which is the gold standard technique for identifying steatosis. The sensitivity of ultrasonography in detecting steatosis varies between 60% and 94% and is dependent on the degree of steatosis. If more sensitive non-invasive technique like CT and MRI could also be used in this study, the prevalence may be higher in diabetes mellitus patients.

5. Conclusion

Non-alcoholic fatty liver disease is an increasingly recognized condition all over the world and its prevalence is increasing in various countries. In Myanmar, it seems to be a common condition and may be increasingly recognized in the future by microvascular complications.

In this study, NAFLD was diagnosed in fifty-eight patients who had NAFLD. This study also reported the prevalence of microvascular complications is higher with NAFLD compared to subjects without NAFLD. Moreover, diabetes patients with NAFLD have 8.879 times risks of neuropathy than those without NAFLD. This study proved that if a diabetes patient has NAFLD, one of the diabetes microvascular complications has already been developed or there is a higher risk of developing microvascular complications soon. The existence of microvascular complications in type 2 diabetes patients will alert clinicians to predict the presence of the NAFLD warranting further evaluation and treatment to prevent the progression of NAFLD. Detecting the presence of fatty liver in diabetes patients at an early stage by non-invasive test, ultrasonography could be used to assess and predict adverse diabetes microvascular complications.

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