THE PREVALENCE OF NONALCOHOLIC FATTY LIVER DISEASES AMONG TYPE 2 DIABETES PATIENTS IN THE WORLD: SYSTEMATIC REVIEW AND META-ANALYSIS

РАСПРОСТРАНЕННОСТЬ НЕАЛКОГОЛЬНОЙ ЖИРОВОЙ БОЛЕЗНИ ПЕЧЕНИ СРЕДИ БОЛЬНЫХ САХАРНЫМ ДИАБЕТОМ 2 ТИПА В МИРЕ: СИСТЕМАТИЧЕСКИЙ ОБЗОР И МЕТААНАЛИЗ

DUNYO BO'YICHA 2-TOIFA DIABET BILAN OG'RIGAN BEMORLAR ORASIDA ALKOGOLSIZ YOG'LI JIGAR KASALLIGINING TARQALISHI: TIZIMLI TAHLIL VA METAANALIZ

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Abstract. Fatty liver is defined as an accumulation of fat in the hepatocytes that exceeds 5% of the weight of the liver and is stored primarily as triglycerides[1]. People with type 2 diabetes appear to have a larger risk of acquiring fatty liver than non-diabetic subjects, and they certainly have a higher risk of developing fibrosis and cirrhosis. Fatty liver disease is thought to affect 70–75 percent of type 2 diabetes patients. The objective of this study is to estimate the pooled prevalence of NAFLD in T2DM patients in the world. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses criteria were used to conduct the systematic review and meta-analysis. A literature search was conducted in PubMed and Web of Science databases for English language papers on NAFLD and Type 2 diabetes that were published between September 2000 and January 2020.

Key words: NAFLD, type 2 diabetes, prevalence

Аннотация. Ожирение печени определяется как скопление жира в гепатоцитах, превышающее 5% веса печени и депонируемое в основном в виде триглицеридов[1]. Люди с диабетом 2 типа, по-видимому, имеют больший риск развития жировой дистрофии печени, чем люди, не страдающие диабетом, и у них, безусловно, более высокий риск развития фиброза и цирроза печени. Считается, что жировая болезнь печени поражает 70–75 процентов пациентов с диабетом 2 типа. Целью данного исследования является оценка общей распространенности НАЖБП у пациентов с СД2 в мире. Для проведения систематического обзора и метаанализа использовались критерии предпочтительных элементов отчетности для систематических обзоров и метаанализа. В базах данных PubMed и Web of Science был проведен поиск литературы на английском языке по НАЖБП и диабету 2 типа, опубликованных в период с сентября 2000 г. по январь 2020 г.

Ключевые слова: НАЖБП, сахарный диабет 2 типа, распространенность.

Annotatsiya. Yog'li jigar kasalligi jigarning 5% dan ortiq yog'ni gepatotsitlarda to'planishi bilan ta'riflanadi va asosan triglitseridlar xisobiga[1]. 2-toifa qandli diabet bilan og'rigan odamlarda diabetga chalinmaganlarga qaraganda jigar yog' bosish xavfi yuqoriroq va ular fibroz va siroz rivojlanish xavfi oshiradi. Yog'li jigar kasalligi 2-toifa diabet bilan og'rigan bemorlarning 70-75 foiziga ta'sir qiladi. Ushbu tadqiqotning maqsadi dunyodagi 2 toifali qandli diabet bor bemorlarda Alkogolsiz jigar yog'li kasalligining umumiy tarqalishini baholashdir. PubMed va Web of Science ma'lumotlar bazalarida 2000-yil sentabrdan 2020-yil yanvarigacha chop etilgan alkogolsiz jigar yog'li kasalligi va 2-toifa diabetga oid ingliz tilidagi maqolalar uchun adabiyot qidiruvi o'tkazildi.

Kalit so'zlar: Alkogolsiz jigar yog'li kasalligi, 2-toifa diabet, tarqalish.

Introduction. Fatty liver is defined as an accumulation of fat in the hepatocytes that exceeds 5% of the weight of the liver and is stored primarily as triglycerides[1]. Fatty liver is widely used in a number of liver disorders, particularly steatosis, steatohepatitis, and fibrosis[1]. Although steatosis usually has a good prognosis, steatohepatitis and fibrosis can develop to cirrhosis[1,2]. By excluding diseases such as HBV and HCV, which may be associated with fatty liver (mainly HCV infection), the entire range of fatty liver abnormalities is now categorized as alcoholic (AFL) or non-alcoholic (NAFL) fatty liver based on ethanol amounts[2,3]. According to EASL, AFL is diagnosed when ethanol intake is ≥30 g per day for men and ≥20 g per day for women and NAFL when ethanol intake is equal to or lower than this value. Because there are no clinical indications or histological findings truly pathognomonic for AFL or NAFL, this difference, depending on the concept that amounts of ethanol under 20 g per day are not poisonous to the liver, is of paramount relevance[1,2]. However, many people do believe that the distinction between AFL and NAFL is arbitrary[2]. An international group of experts recently recommended that NAFLD be renamed metabolic (dysfunction) associated fatty liver disease (MAFLD)[4]. As a result of the proposed name change, an international consortium of 32 specialists from 22 countries was formed to conduct in-depth evaluations of the accuracy of the fatty liver disease definition and the spectrum of heterogeneity. This collaboration presented a thorough concept for redefining fatty liver disease that was simple and easy to implement. They proposed a new practical and clinically based definition of MAFLD that includes "positive criteria" for diagnosis, assures MAFLD is a distinct entity, and avoids the major limitations of the current "anti-definition". These considerations are based on the presence of one of the three criteria, weight or obesity, type 2 diabetes mellitus, or evidence of metabolic abnormalities, and the identification of steatosis using various modalities (imaging, blood biomarker, or histology)[5]. The frequency of fatty liver disease in the general population has been estimated to be between 15 and 30 percent in various nations and is almost certainly increasing[6-7]. People with type 2 diabetes appear to have a larger risk of acquiring fatty liver than non-diabetic subjects, and they certainly have a higher risk of developing fibrosis and cirrhosis[8-9]. Fatty liver disease is thought to affect 70–75 percent of type 2 diabetes patients[10].

Patients with fatty liver are much more susceptible to have metabolic syndrome markers such as obesity, type 2 diabetes, hyperlipidemia, and hypertension. T2DM considered to be the most important risk factor for NAFLD and non-alcoholic steatohepatitis (NASH), and also the most important clinical predictor of poor clinical outcomes such advanced hepatic fibrosis and mortality[11].

The relation between fatty liver disease and type 2 diabetes mellitus (T2DM) has been well identified, which could be described by insulin resistance and compensatory hyperinsulinemia in fatty liver disease progressing to malfunctioning lipid metabolism and hepatic triglyceride (TG) accumulation in T2DM12 or -cell dysfunction in T2DM[12]. The prevalence of fatty liver disease in East Asia has been reported to be 52.04 % (95 % CI: 45.37–58.55%)[11]. Uzbekistan is included in this research as an East Asian country. There has never been a study on the prevalence of fatty liver disease in the diabetic population of Uzbekistan. Fatty liver disease prevalence rate in Uzbekistan climbed from 27.0 % in 2007 to 37.1 % in 2014, ranking first among liver diseases[13].

The objective of this study: to estimate the pooled prevalence of NAFLD in T2DM patients.

Materials and methods. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses criteria were used to conduct the systematic review and meta-analysis. A literature search was conducted in PubMed and Web of Science databases for English language papers on NAFLD and Type 2 diabetes that were published between September 2000 and January 2020. Two investigators independently assessed eligibility and extracted data, and a meta-analysis was used to synthesis the results. The following keywords were used in the literature search: (“NAFLD”, “Type 2 diabetes”, “prevalence”).

Eligibility criteria. A review article or abstract; the study did not identify patients with NAFLD; the study was not in English; the study reported type 1 diabetes.

Data extraction. Two investigators independently assessed article eligibility and extracted data from papers that were found to be eligible. The following information was gathered: first article

title, author, journal name, country, year of publication, study design, subject characteristics, diabetes and fatty liver diagnostic technique, sample size, gender, and prevalence of NAFLD in T2DM.

Statistical analyses. The number of positive fatty liver subjects divided by the total number of subjects examined was used to estimate the prevalence of fatty liver disease. To account for uncertainty in pooled estimates due to research heterogeneity, overall prevalence estimates were calculated using the random effect meta-analyses approach. Individual study proportions, as well as the pooled effect, were analyzed using a 95% confident interval (CI). We created the Index of Inconsistency(I^2) to analyze study heterogeneity.

Ethical approval: As this was a review of studies/data which had already been published or were in the public sphere, because of these reasons for our systematic review and meta-analysis did not require ethical approval.

Results. *General assessment:* Through online databases, a total of 1809 publications were found, including 713 from Web of Science and 1096 from PubMed. After the exclusion of duplicate and irrelevant studies based on title and abstract screening, 74 full texts were extracted and reviewed for eligibility criteria in detail. There were 15 papers that passed the qualifying criteria and were included in both qualitative and quantitative analyses.

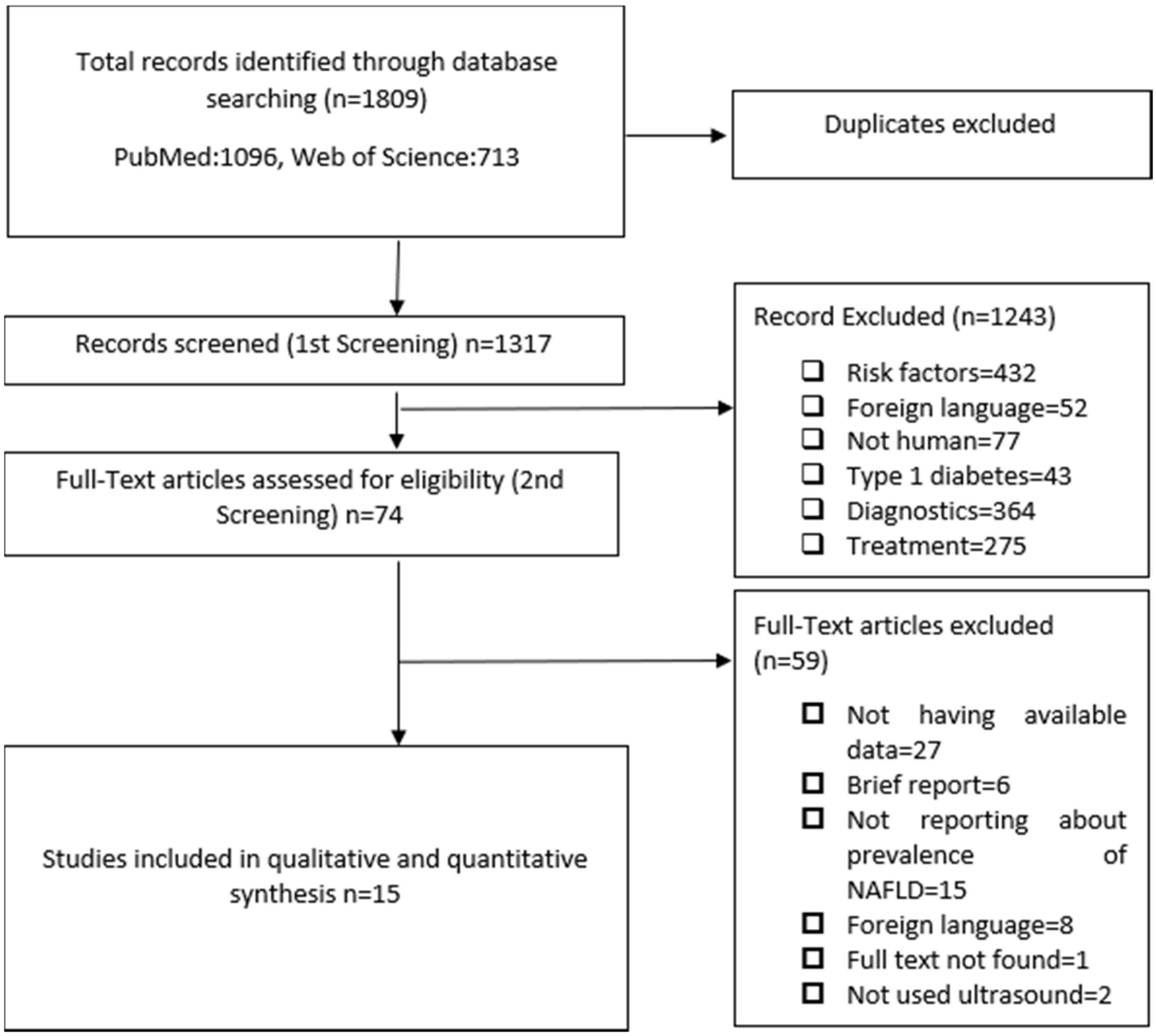

Figure 1 outlines the schematic flow diagram of the study detection and inclusion procedures.

Study characteristics:

The following table 1 shows the characteristics of the 15 eligible studies conducted in 13 countries.

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Table 1. Characteristics of eligible studies for systematic review and meta-analyses

First author	Year of publication	Region	Study design	Diagnostic criteria of fatty liver	T2DM patients with fatty liver	Sample size	Prevalence %
Mubashir	2017	Pakistan	Cross sect.	Ultrasound	78	100	78
Marcin	2013	Poland	Cross sect.	Ultrasound	70	100	70
Bo-Yeong	2014	South Korea	Cross sect.	Ultrasound	586	929	63
Karel	2015	Czech Rep.	Retrospective Cohort study	Ultrasound	142	180	79
Giovanni	2007	Italy	Cross sect.	Ultrasound	1372	1974	69.5
Mohan	2009	India	Cross sect.	Ultrasound	292	541	54
Sheela	2015	India	Cross sect.	Ultrasound	71	109	65
Ahmad	2015	Sudan	Cross sect.	Ultrasound	84	167	50.3
Cristina	2016	Romania	Cross sect.	Ultrasound	300	381	78.7
Herath	2018	Sri Lanka	Retrospective Cohort study	Ultrasound	140	223	62.7
Alexandra	2014	Romania	Cross sect.	Ultrasound	303	348	87.1
Belay	2018	Ethiopia	Cross sect.	Ultrasound	70	96	73
Abdullah	2018	Saudi Arabia	Cross sect.	Ultrasound	178	245	72.65
M. Yi	2016	China	Cross sect.	Ultrasound	1752	3861	45.37
Amrendra	2018	USA	Cross sect.	Ultrasound	117	210	55.71

A total of 9461 T2DM patients were involved, of which 5555 were identified with fatty liver disease. Also, among the 15 eligible studies, 2 were retrospective Cohort study and 13 were cross-sectional study.

Pooled prevalence of fatty liver disease.

The pooled prevalence of fatty liver disease was seen from 45.3% to 87% of T2DM patients in the trials that were included. The significant heterogeneity (I^2=0%, P<1) was observed among the eligible studies, a random-effects model was used to estimate the pooled prevalence.

Fatty liver disease was found that the prevalence has been estimated 60.89% (95% CI:59.95-61.83%) among T2DM patients. Figure 2 presents the detail. The publication bias assess graphically by a Funnel plot of all included studies. Figure 3 was illustrated graphically through a funnel plot of studies by a near symmetrical distribution of prevalence reported. This means there is little effect of publication bias on the result of meta-analyses.

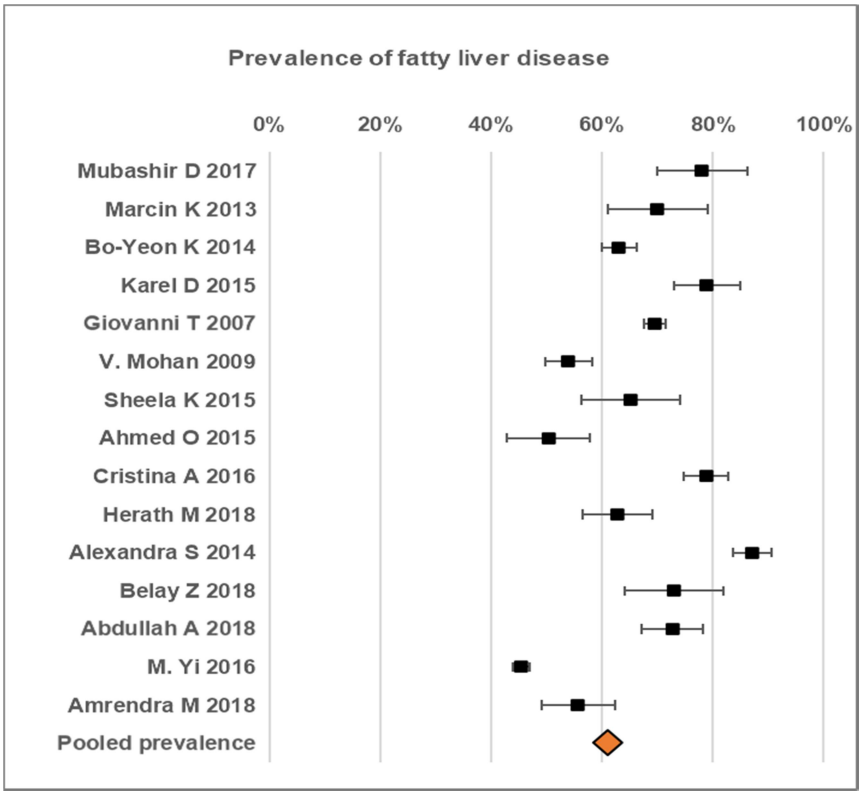

Fig. 2 Forest plot of 15 prevalence studies and pooled prevalence using random effect model.

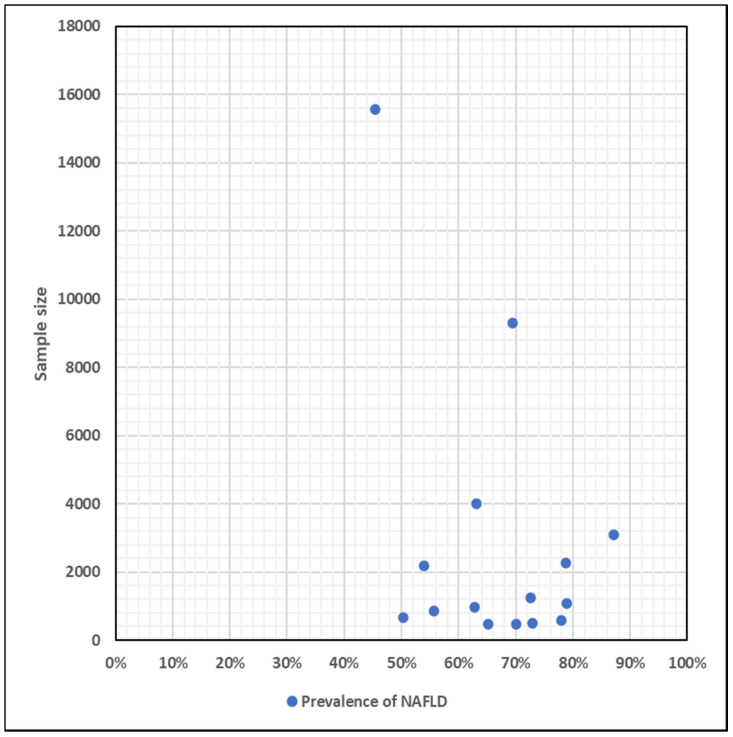

Fig. 3 Funnel plot to assess publication bias

Discussion. According to a previous study, the fatty liver disease increased from 27.0% in 2007 to 37.1% in 2014 in the general population in Uzbekistan and ranked first among liver disease[13]. The other report of meta-analyses has estimated that the prevalence of NALFD in East Asia was 52.04% (95% CI 45.37–58.55%) among type 2 diabetes patients[11]. In a recent meta-analysis including 80 studies and 20 countries the global prevalence of NAFLD among type 2

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diabetes mellitus was 55.5% (95% CI: 47.3-63.7). This the global prevalence of NAFLD almost similar to our study, but this meta-analysis has been estimated only for non-alcoholic fatty liver disease. In our research, we did not exclude heavy alcohol consumption therefore we say that the result of our study belongs to fatty liver disease (including NAFLD and AFLD). Also, another clinic-based study recorded a similar result to our study that the prevalence of NAFLD was 55,71% in type 2 diabetes patients in USA[14]. Alexander and his colleagues indicated the prevalence of the fatty liver disease among type 2 diabetes patients was 30.8%[15]. This research was conducted in outpatient clinics in Kazakhstan which neighbor country of Uzbekistan. The results of this study are significantly less than the results of our study.

According to our meta-analysis which included 15 studies and 13 countries that pooled prevalence has been estimated at 60.89% (95% CI:59.95-61.83%) and ranged from 45.3% to 87.0% *(Table 1)*. Also, our meta-analyses suggested that the highest prevalence of NALFD has been estimated with 87% in Romania[15].

The high prevalence of fatty liver disease among hospitalized diabetic patients in Uzbekistan may be associate with the following factors:
this study was conducted in two urban area where a most of the population lead a sedentary lifestyle
the Uzbek diet is generally high in carbohydrates
the Uzbekistan national food is rich in fatty meats such as lamb and beef (high sources of animal cholesterol)

This research has a number of limitations that should be highlighted. First, this study was a cross-sectional retrospective design, which did not permit the determination of causality. Second, in our research the diagnosis of fatty liver disease was based on ultrasound imaging. It has been reported that the presence of>30% fat on liver biopsy is optimal for ultrasound detection of fatty liver disease, even if the fat infiltration is <30% in that case ultrasound examination is not totally sensitive[16]. The gold-standard technique for the diagnosis of fatty liver is liver biopsy[17], but it is expensive and impossible to perform routinely in a large epidemiological study. Another disadvantages of liver biopsy are invasive and may give the sampling error. Third, this study was conducted in the urban area in Uzbekistan and did not include rural areas. For this reason, our result only applicable to the prevalence of fatty liver in urban areas in Uzbekistan.

Conclusion. According to our meta-analysis which included 15 studies and 13 countries that pooled prevalence has been estimated at 60.89% (95% CI:59.95-61.83%) and ranged from 45.3% to 87.0%.

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