Annals of Medical Research
DOI: 10.5455/annalsmedres.2018.07.137 2018;25(4)564-8

Original Article

# The prevalence and predictors of prediabetes in the patients on liver transplant wait list

Omercan Topaloglu[1], Bahri Evren[1], Saim Yologlu[2], Selale Sahin[3], Cuneyt Kayaalp[4], Ibrahim Sahin[1]

[1]Inonu University, Faculty of Medicine Department of Endocrinology, Malatya, Turkey
[2]Inonu University, Faculty of Medicine Department of Biostatistics, Malatya, Turkey
[3]Public Health Center, Malatya, Turkey
[4]Inonu University, Faculty of Medicine Department of General Surgery, Malatya, Turkey



**Abstract**

**Aim:** Studies addressing the prevalence of prediabetes among liver transplantation (LT) candidates are limited. We aimed to investigate the prevalence and predictors of prediabetes in the patients on LT wait list.

**Material and Methods:** One hundred one adult patients on LT wait list were included. Patients with known diabetes were excluded. Clinical, demographic and laboratory features were analyzed retrospectively. The patients were grouped by fasting blood glucose (FBG), age, gender, body mass index (BMI), and other clinical parameters.

**Results:** Mean age of the patients was 47.98 ± 14.53; and 63.3% were males. Prediabetes and new-onset diabetes mellitus were diagnosed in 34(33.6%) and 6(5.9%) of the patients. Mean age was significantly higher in prediabetes group comparing to normal FBG. 52.47% (n = 53) of the patients was obese, 27.7% (n = 28) overweight, 19.8% in normal weight. The distribution of BMI subgroups was similar in FBG subgroups (p = 0.447). There were significant positive correlations between age, and BMI or FBG (p = 0.021 and p = 0.002, respectively). Being older (≥ 40 years-old) was found to be a predictor for prediabetes (p = 0.010, Odds Ratio = 4.986). BMI was not a predictor for prediabetes (p = 0.151).

**Conclusions:** Our results suggested that the prevalence of prediabetes was increased in patients on LT wait list. Age but not BMI seems to be a significant predictor of prediabetes.

**Keywords:** Prediabetes; Liver Transplantation; Liver Failure; Diabetes Mellitus.

## INTRODUCTION

Liver transplantation (LT) is an important treatment option for those indicated. However, we should consider risks (such as post-transplant immunosuppression and diabetes, or infections) and benefit (increased quality of life) before LT. In patients on LT wait list, several preoperative screening tests should be worked up, such as complete blood count and serum biochemistry including fasting blood glucose (FBG).

Prediabetes may be defined by impaired fasting glucose (IFG), impaired glucose tolerance (IGT) or HbA1c level of 5.7-6.4% (1). It has been increasingly diagnosed in clinical settings and studied in clinical trials. The patients with prediabetes should be followed-up with serial glucose monitoring and have increased risk to develop type 2 diabetes mellitus (DM).

Several studies investigated the metabolic profile (such as FBG and HbA1c) of the patients on wait list of renal, lung or liver transplant (2-5). It has been shown that the glycemic profile of the patients on transplant wait list might have effect on graft survival and the prevalence of post-transplant diabetes (5-10).

However, the number of studies examining the prevalence of prediabetes in patients on LT wait list is limited (11), and the predictors of prediabetes in these patients have not been well studied. We aimed to investigate the prevalence and predictors of prediabetes in the patients on LT wait list.

## MATERIALS AND METHODS

The patients on LT wait list between January 2016 and January 2018in our hospital were evaluated for the study.

**Received:** 19.07.2018 **Accepted:** 02.08.2018 **Available online:** 07.08.2018
**Corresponding Author:** Omercan Topaloglu, Inonu University, Faculty of Medicine Department of Endocrinology, Malatya, Turkey
**E-mail:** drhomercan@hotmail.com

A total of 101 adult patients without known history of DM were included in the study. Data of the patients were analyzed retrospectively from the electronic files of the patients. Patients with missing data, taking antidiabetic medication, with a personal history of DM, gestational DM, LADA (Latent Autoimmune Diabetes of Adults) or MODY (Maturity Onset Diabetes of Young), or aged less than 18 were excluded. All our patients were on LT wait list for the first transplantation.

All protocols of our study were approved by the local ethics committee of our institution before the study began, and that the protocols conformed to the ethical guidelines of the 1975 Helsinki Declaration.

Clinical and demographic features of the patients such as gender, age, and accompanied chronic illnesses were recorded. Body weight and height were noted as kg and cm, respectively, by using electronic files. BMI was calculated by weight/(height)2. In our routine clinical practice, preoperative FBG levels were measured from venous plasma after an overnight fasting, and recorded as mg/dL. The patients were mainly grouped according to FBG: < 100 mg/dL, 100-125 mg/dL, ≥ 126 mg/dL. The patients having FBG of 100-125 mg/dL were diagnosed as prediabetes, ≥ 126 as new-onset DM, < 100 as normal (1). The patients were also evaluated for differential diagnosis of type 1 or 2 DM by clinical and metabolic phenotype. Clinical and metabolic phenotype of any of the patients was not consistent with type 1 DM or LADA, all of them were diagnosed as type 2 DM.

The patients were also grouped by age (< 40 vs 40-64 vs ≥ 65), gender, BMI (< 25 vs 25-29.9 vs ≥ 30), accompanied chronic illness (chronic viral hepatitis such as hepatitis B or C vs other chronic diseases), drug use (antiviral vs other). The patients were also sub-grouped by the indication for transplantation as acute liver failure, chronic viral hepatitis, and other diseases.

**Statistical Analysis**

Analysis of the study data was performed using SPSS version 22.0 (IBM Corporation, Armonk, New York, USA). The conformity of univariate data to normal distribution was evaluated with the Shapiro-Wilk test. We compared categorical variables with each other by using Pearson Chi-square test. In comparing more than two independent groups according to quantitative data, Kruskal-Wallis H Tests for nonparametric analysis were used, and Conover Test was used for Post Hoc analyses. To analyze the correlations of variables with each other, we used Pearson correlation test. Logistic regression analysis was used to determine the risk groups for parameters affecting development of prediabetes. Odds Ratio (OR) was used with 95% confidence intervals (CI) to show that risk groups had how higher risk than the other subjects. Quantitative variables were shown as mean ± standard deviation (SD), categorical variables as n(%) in tables. A value of $p < 0.05$ was accepted as statistically significant.

## RESULTS

Of the patients, 63.3% was male, and 36.6% was female. Mean age of the patients was 47.98 ± 14.53. Prediabetes and new-onset type 2 DM were diagnosed in 34 (33.6%) and 6 (5.9%) of the patients; normal FBG was found in 61 (60.4%) of the patients.

If we analyze the patients' results according to different FBG subgroups (< 100, 100-125, ≥ 125 mg/dL), gender distribution, mean weight, height and BMI were similar in different FBG groups. However, mean age was significantly different ($p = 0.001$). And it was based on the difference between prediabetes and normal FBG, and between DM and normal FBG. As expected, mean FBG was significantly higher in DM group (Table 1). Mean FBG of all patients was 102.82 ± 38.66.

If we evaluate the patients according to age groups (< 40, 40-64, ≥ 65 year-old), the percent of the patients was 28.7%, 59.4%, and 11.9% in age groups of < 40, 40-64, and ≥ 65, respectively. The percent of patients of < 40 years-old was significantly higher in the patients with normal FBG, however, the percent of patients aged between 40 and 64 was significantly higher in prediabetes group ($p = 0.007$). Chronic HBV and HCV were found in 39.6% and 7% of the patients, respectively. A total of 46,6% of the patients had chronic viral hepatitis, and the remainder (53.4%) had other chronic diseases. The frequency of prediabetes was 32.5% in chronic HBV, 57.1% in chronic HCV, 31.5% in other chronic disease group ($p = 0.690$). Antiviral drug usage was found in 7.9% of the patients. The distribution of FBG subgroups were similar in the patients having antiviral drug or not ($p=0.482$). The indication for transplantation was acute liver failure in 12.9, chronic viral hepatitis in 39.6, and other chronic diseases in 47.5% of the patients, respectively. In a total of 87.1% of the patients, liver transplantation were indicated for chronic liver failure. The prevalence of prediabetes was 15.4% in acute liver failure, 37.5% in chronic viral hepatitis, and 35.4% in other indications for transplantation ($p= 0.372$).

More than half (52.47%) of the patients were obese (n = 53), 27.7% (n = 28) overweight, 19.8% was in normal weight. The prevalence of obesity was 59.45 and 48.4 % in female and male patients, respectively. Mean age, FBG and BMI were similar in both genders ($p = 0.07$, $p = 0.085$, and $p = 0.969$, respectively). The distribution of BMI subgroups was similar between FBG subgroups ($p = 0.447$).

Logistic regression analysis was performed to show the predictors for prediabetes. Being older (≥ 40 years old) was found to be predictor for prediabetes ($p = 0.010$, OR: 4.986). Surprisingly, BMI could not be observed as a predictor for prediabetes in these patients ($p = 0.151$) (Table 2).

There was significant positive correlation between age and BMI, age and FBG ($p = 0.021$ and $p = 0.002$, respectively) (Table 3).

**Table 1. Baseline characteristics according to FBG groups**

| | | | FBG (mg/dL) | | |
|---|---|---|---|---|---|
| **Variables** | **<100 (n=61)** | **100-125 (n=34)** | **≥126 (n=6)** | **Total (n=101)** | **p value** |
| **Gender (m/fm)** | 34/27 | 26/8 | 4/2 | 64/37 | 0.126 |
| | | | **mean±SD** | | |
| **Age (years)** | 44±14.37 | 52.85±13.19 | 60.83±6.67 | 47.98±14.53 | 0.001 |
| **Weight (kg)** | 81.57±16.10 | 78.83±15.44 | 78.90±10.80 | 80.49±15.55 | 0.692 |
| **Height (cm)** | 165.89±7.22 | 167.74±8.48 | 164.83±9.15 | 166.45±7.75 | 0.686 |
| **BMI (kg/m2)** | 29.58±5.14 | 28.08±5.39 | 29.43±6.30 | 29.07±5.28 | 0.453 |
| **FBG (mg/dL)** | 86.07±13.28 | 111.97±7.75 | 221.33±80.80 | 102.82±38.66 | 0.001 |

**Table 2. Univariate logistic regression showing predictors for prediabetes**

| **Variables** | **OR (95% CI)** | **p value** |
|---|---|---|
| **Age (≥40 or <40)** | 4.986 (1.46-17.03) | 0.010 |
| **Gender (male or female)** | 2.580 (0.948-7.024) | 0.064 |
| **BMI (≥30 or <30)** | 0.496 (0.191-1.292) | 0.151 |
| **Chronic illness (others or viral hepatitis)** | 1.996 (0.711-5.605) | 0.189 |
| **Drug (no or antiviral)** | 0.777 (0.161-3.749) | 0.753 |
| **Chronicity (chronic or acute)** | 2.388 (0.423-13.487) | 0.325 |

**Table 3. Correlation analysis showing correlations between variables**

| | | **Age** | **BMI** | **Weight** | **Height** | **FBG** | |
|---|---|---|---|---|---|---|---|
| **Age** | **r** | 1 | 0,229 | 0,228 | 0,013 | 0,306 | |
| | **p** | | 0,021 | 0,022 | 0,899 | 0,002 | |
| | **n** | 101 | 101 | 101 | 101 | 101 | |
| **BMI** | **r** | | 1 | 0,873 | -0,164 | -0,111 | |
| | **p** | | | 0,001 | 0,101 | 0,270 | |
| | **n** | | 101 | 101 | 101 | 101 | |
| **Weight** | **r** | | | 1 | 0,331 | -0,106 | |
| | **p** | | | | 0,001 | 0,293 | |
| | **n** | | | 101 | 101 | 101 | |
| **Height** | **r** | | | | 1 | 0,014 | |
| | **p** | | | | | 0,887 | |
| | **n** | | | | 101 | 101 | |
| **FBG** | **r** | | | | | 1 | |
| | **p** | | | | | | |
| | n | | | | | 101 | |

## DISCUSSION

In this study, we analyzed the patients on LT wait list to observe the prevalence and predictors of prediabetes. Our findings showed that prediabetes and new-onset DM were diagnosed in 33.6% and 5.9% of the patients. Mean age was significantly higher in these prediabetes and diabetes subgroups. More than half (52.47%) of the patients were obese, 27.7% overweight, 19.8% was in normal weight. The distribution of BMI subgroups was similar between FBG subgroups. Only being older (≥ 40 years old) was found to be a significant predictor for prediabetes. However, BMI could not be observed as a significant predictor for prediabetes. There were significant positive correlations between age with BMI and FBG.

The prevalence of impaired glucose tolerance in general population was reported as 6.7% in 2015 report of International Diabetes Federation (12). And, according to national statistics report in USA, the prevalence of prediabetes was 37% (13). NHANES (National Health and Nutrition Examination Survey) North America cohort showed that a high prevalence of prediabetes and impaired fasting glucose (IFG) was found as 34.62% and 19.4%, respectively (14). In Turkey, the prevalence of prediabetes was found as 6.7% and 30.8% in two

comprehensive epidemiological studies (TURDEP 1 and TURDEP 2) designed 10 years apart (15,16). We found the frequency of prediabetes as 33.6% in patients on LT wait list, in concordance with general population. However, we evaluated prediabetes only by FBG. In TURDEP 2 study, the prevalence of prediabetes was found as 26.4% according to HbA1c only, 30.8% if FBG and 2nd hour glucose after oral glucose tolerance test (OGTT) were evaluated together (16). However, the prevalence of prediabetes was 22.9% based on only FBG in TURDEP 2. Indeed, in our study sample, we found a higher prevalence of prediabetes according to FBG than TURDEP 2. In another study, FBG led to a diagnosis of prediabetes in increased number of patients (15). Similarly, use of combination of FBG, 2nd hour glucose after OGTT and HbA1c provided higher number of diagnosis of prediabetes (17). We would find a higher frequency of prediabetes in our patients, if we could analyze 2nd hour plasma glucose after a 75 gram OGTT and HbA1c level. In patients on LT wait list, unfortunately, OGTT or HbA1c measurements are not routine in preoperative screening. In one study including the patients with renal failure on renal transplant wait list, Guthoff et al. showed that the prevalence of prediabetes and new DM was 30% and 3%, respectively (18). They used both FBG, 2nd hour glucose after OGTT and HbA1c in the evaluation of DM and prediabetes. Hackman et al. investigated the prevalence of new DM, and prediabetes in the patients on lung transplantation wait list using OGTT (2). They found a higher prevalence of new DM as 7.3% and lower prediabetes as %15.2. They also found a poor correlation between HbA1c and OGTT results. These differences in the studies analyzing the patients on different organ transplantation list may be based on the distinct nature and course of underlying diseases.

In general, IFG and impaired glucose tolerance (IGT) were shown to progress to overt diabetes with a rate of 25% in 5 years (19). This may be accelerated by organ transplantation and immunosuppressive drugs. Indeed, prediabetes was found to be associated with 4.5 fold increased risk of post-transplant diabetes (5). Besides, other similar risk factors may have a role in the development of prediabetes and DM, such as genetic features, environmental factors, defect in insulin secretion, and insulin resistance (20,21). Increased age is an absolute risk factor for DM, and the risk of prediabetes was suggested to increase with increasing age (12). In our study, we found a positive correlation between FBG and age. Moreover, we showed that being older than 40 years was a significant predictor for prediabetes. Increased age was shown to be a risk factor for type 2 DM. We also showed that age was positively correlated with BMI. Increasing BMI with increased age might also contribute to the development of prediabetes in the patients ≥ 40 years old. However, we could not observe BMI as a significant predictor for prediabetes. Guthoff et al. investigated 138 patients on renal transplant wait list and they found that BMI and age were independent risk factors for metabolic phenotype (18). The prevalence of prediabetes was increased with increasing BMI in that study. However, gender, positive family history for DM, or waiting time for transplantation was not found as a predictor. In our study, mean FBG and BMI were similar in both genders. Similarly, gender was not a significant predictor for prediabetes.

We found that a significant part of the patients was obese (52.47%), and only 19.8% had normal body weight. The prevalence of obesity was found to increase up to 35% in TURDEP-II study in Turkey (15,16). In our study sample, obesity was more prevalent than general population. Although higher prevalence of obesity was observed in our patients comparing to general population, similar frequency of prediabetes was similar with general population. Under normal situations, the liver provides a major part of glucose production (80-85%) mainly by glycogenolysis and later gluconeogenesis. In acute or chronic liver disease, glucose production decreases with decreasing functions and/or mass of the liver. Moreover, due to decreased degradation of insulin by failed liver, hyperinsulinemia may ensue (22). Therefore, if a comorbid situation such as an infection accompanies, the patient with liver failure may prone to hypoglycemia. As a result, decreased glucose production in liver failure may mask or blunt the increments in FBG, and preclude such a higher prevalence of prediabetes in these patients. Additionally, in the patients with liver failure, formation of ascites, edema, pleural effusion, or hepatosplenomegaly may contribute to increased body weight. However, sarcopenia, muscle wasting, vomiting or malnutrition may cause to a change in phenotype. Therefore, measurement of BMI may not be a reliable tool in evaluating adiposity in these patients. As a result, the variability of BMI may contribute to the discordance between the prevalence of BMI and prediabetes in our sample.

We found that the prevalence of new-onset type 2 DM was 5.9% in our sample, and somewhat lower than general population. However, we did not include the patients with known DM. Hergesell et al. investigated the prevalence of DM in 377 patients on renal transplant wait list, and found as 12.2% (3). Of diabetic patients, 19.5% was diagnosed as type 1 DM, the remainder as type 2 DM. They showed that more than half of the patients with type 2 DM, and finally 5.3% of all patients was diagnosed as new-onset type 2 DM during waiting transplantation. Guthoff et al. found the prevalence of new-onset DM in the patients on renal transplant wait list as low as 3% in their study (18). Hackman et al. found the prevalence of new-onset DM in the patients on lung transplantation wait list as 7.3% (2). Given both our results and these studies, the prevalence of new-onset DM in the patients on different transplant wait list was not as high as general population. Similar to the mechanisms proposed for prediabetes, decreased glucose production due to defective gluconeogenesis might preclude the real frequency of DM in the patients on renal and liver transplant wait list. The same mechanisms could shift the diagnosis from DM to prediabetes by preventing the increase of FBG to a threshold for DM providing the diagnosis of DM. Unfortunately, therapeutic intervention

to institute normoglycemia should be done according to real FBG levels.

We know that prediabetes increases the risk of development of post-transplant diabetes, and DM increases perioperative morbidity in transplant patients. Therefore, the patients on LT wait list should be screened by FBG, and endocrinologists should be in contact with transplant surgeons for the evaluation of glycemic status. Then, those with overt DM should be treated with accordingly; the patients with FBG in prediabetic level should be evaluated by OGTT or HbA1c. However, medications preventing the progression of prediabetes to type 2 DM and some oral antidiabetic drugs used in DM are contraindicated in these patients due to liver disease. Eventually, correcting liver failure by LT may solve the underlying pathophysiology.

**Limitations and Strengths**

We could not perform OGTT or measure HbA1c level in our patients due to the retrospective nature of the study. We diagnosed prediabetes by using only FBG of the patients. In the patients with liver failure, formation of ascites, edema, pleural effusion, and hepatosplenomegaly, or sarcopenia, muscle wasting, vomiting and malnutrition may cause to change in phenotype and have different effects on BMI in these patients. Therefore, BMI may not be a reliable tool in evaluating adiposity in these patients. This variability of BMI may contribute to the discordance between the prevalence of BMI and prediabetes in our sample.

## DISCUSSION

Our findings suggested that prediabetes was slightly increased in the patients on LT wait list compared to normal population. Furthermore, prevalence was especially higher in patients with chronic liver failure. Being older (≥40 years-old) was a significant predictor for prediabetes. However, BMI seems to have no significant effect on prediabetes, and not be a reliable tool in evaluating adiposity in these patients due to the factors mentioned before.

*Acknowledgements: We are thankful to all authors for contributions in data collection, statistics, article writing and editing.*
*Competing interests: The authors declare that they have no competing interest.*
*Financial Disclosure: There are no financial supports*
*Ethical approval: All protocols of our study were approved by the local ethics committee of our institution before the study began, and that the protocols conformed to the ethical guidelines of the 1975 Helsinki Declaration.*

## REFERANS

1. Classification and diagnosis of diabetes: standards of medical care in diabetes 2018. Diabetes Care. 2018;41:S13-S27.
2. Hackman KL, Snell GI, Bach LA. An unexpectedly high prevalence of undiagnosed diabetes in patients awaitinglung transplantation. J Heart Lung Transplant. 2013;32:86-91.
3. Hergesell O, Zeier M. Underdiagnosis of diabetes mellitus in chronic dialysis patients on the renaltransplant waiting list. Transplant Proc. 2003;35:1287-9.
4. Woodward RS, Schnitzler MA, Baty J, et al. Incidence and cost of new onset diabetes mellitus among U.S. wait-listed and transplanted renal allograft recipients.Am J Transplant. 2003;3:590-8.
5. Tillmann FP, Radtke A, Rump LC, et al. Effect of prediabetes on allograft survival and evolution of new onset diabetes after transplant in deceased-donor kidney transplant recipients during long-term follow-up. Exp Clin Transplant. 201715:620-6.
6. Shin JI, Palta M, Djamali A, et al. Higher pretransplantation hemoglobin a1c is associated with greater risk of posttransplant diabetes mellitus.Kidney Int Rep. 2017;2:1076-87.
7. Nijpels G, Popp-Snijders C, Kostense PJ, et al. Fasting proinsulin and 2-h post-load glucose levels predict the conversion to NIDDM in subjects with impaired glucose tolerance: the Hoorn Study. Diabetologia. 1996;39:113-8.
8. Gerstein HC, Santaguida P, Raina P, et al. Annual incidence and relative risk of diabetes in people with various categories of dysglycemia: a systematic overview and metaanalysis of prospective studies. Diabetes Res Clin Pract. 2007;78:305-12.
9. Joss N, Staatz CE, Thomson AH, et al. Predictors of new onset diabetes after renal transplantation. Clin Transplant. 2007;21:136-43.
10. Chakkera HA, Weil EJ, Swanson CM, et al. Pretransplant risk score for new-onset diabetes after kidney transplantation. Diabetes Care. 2011;34:2141-5.
11. Perito ER, Lustig RH, Rosenthal P. Prediabetes in pediatric recipients of liver transplant: mechanism and riskfactors.J Pediatr. 2017;182:223-31.
12. The Global Picture: International Diabetes Federation Diabetes Atlas 7th Edition, 2015:61-62. www.idf.org/idf-diabetes-atlas-seventh-edition-2015.
13. CDC national diabetes statistics report 2014 availible in http//www.cdc.gov/diabetes/pubs/statsreport14/national- diabetes-report-web.pdf
14. Karve A, Hayvard RA. Prevalence, diagnosis, and treatment of impaired fasting glucose and impaired glucose tolerance in nondiabetic U.S. adults Diabetes Care. 2010:33;2355-9.
15. Satman I, Yilmaz T, Sengül A. et al. Population-based study of diabetes and risk characteristics in Turkey: results of the turkish diabetes epidemiology study (TURDEP) Diabetes Care. 2002;25:1551-6.
16. Satman I, Omer B, Tutuncu Y, et al. Twelve-year trends in the prevalence and risk factors of diabetes and prediabetes in Turkish adults. Eur J Epidemiol. 2013;28:169-80.
17. Okosun IS, Seale JP, Lyn R, et al. Improving detection of prediabetes in children and adults: using combinations of blood glucose tests. Front. Public Health. 2015;3:260.
18. Guthoff M, Vosseler D, Langanke J, et al. Diabetes mellitus and prediabetes on kidney transplant waiting list-prevalence, metabolic phenotyping and risk stratification approach.PLoS One. 2015;10:e0134971.
19. Nathan DM, Davidson MB, DeFronzo RA, et al. Impaired fasting glucose and impaired glucose tolerance: implications for care. Diabetes Care. 2007;30:753-9.
20. Bansal N. Prediabetes diagnosis and treatment: a review. World J Diabetes. 2015;6:296-303.
21. Kanat M, DeFronzo RA, Abdul-Ghani MA. Treatment of prediabetes. World J Diabetes. 2015;6:1207-22.
22. Johnson DG, Alberti KG, Faber OK, et al. Hyperinsulinism of hepatic cirrhosis: diminished degradation or hypersecretion? Lancet. 1977;1:10-3.