MICRO LABS LIMITED

Diabetes Update

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Dear Doctor,

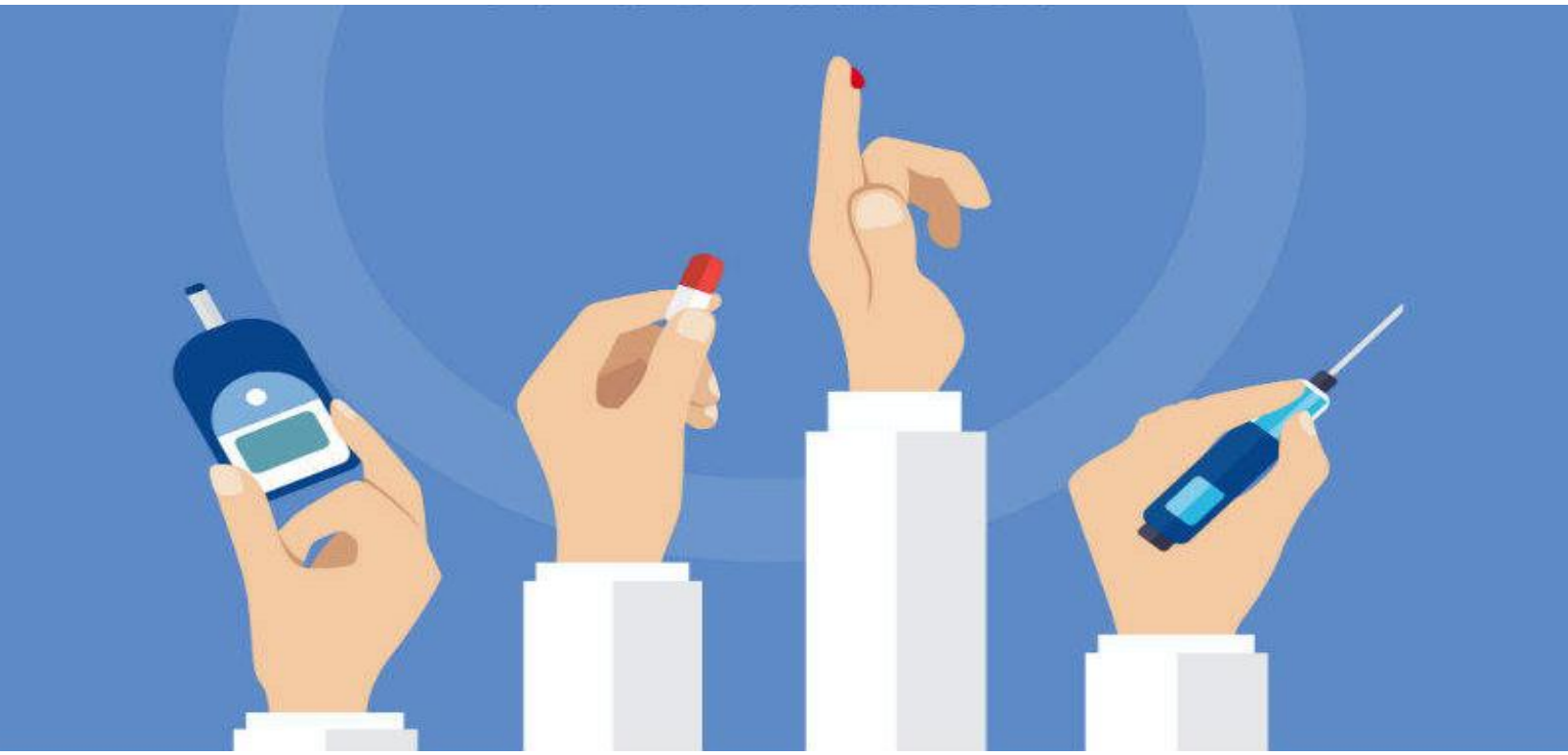
Greetings from Micro Labs Limited. We are happy to bring you "DIABETES UPDATE" which contains latest and interesting news in the field of Diabetes and Endocrinology.

- Dose-dependent and Time-varying effect of statin use and risk of type 2 diabetes
- Association between Glycemic control and diabetic foot ulcer outcomes: A meta-analysis
- Continuous Glucose Monitoring in Pregnancy: CONCEPTT trial

Should you require any specific article or medical information, please feel free to contact us at medicalservices@microlabs.in

Looking forward to your valuable feedback

Best Regards,
Medical Team, Micro Labs Limited



Dose-dependent and Time-varying effect of statin use and risk of type 2 diabetes

The American College of Cardiology/American Heart Association (ACC/AHA)'s 2018 guidelines recommend the use of statins in the treatment of dyslipidemia and to prevent atherosclerotic cardiovascular disease (ASCVD) events. This study evaluated the effect of statin use on new-onset type 2 diabetes among individuals without atherosclerotic cardiovascular disease (ASCVD).

A total of 13,698 patients (statin users 5273, non-statin users 5273) aged 40–74 years, newly diagnosed with dyslipidemia but without any history of diabetes or ASCVD, were selected in 2005. We followed up the final sample until 2013 and evaluated the cumulative incidence of type 2 diabetes. We used extended Cox regression models to estimate the time-varying adjusted hazard ratios of statin use on new-onset type 2 diabetes. We performed further analyses based on the cumulative defined daily dose of statin received per year to evaluate the degree of risk compared to non-statin users.

Over the mean follow-up period of 7.1 years, during follow-up, 3034 patients developed type 2 diabetes: 1871 statin users (61.67%) and 1163 non-users (38.33%). The overall incidence of type 2 diabetes was 40.52 per 1000 person-years (51.95 for statin users, 29.93 for non-users) (Table).

Variables	**Statin group (N = 5273)**	**Non-statin group (N = 5273)**
Follow-up period (years), mean (SD)	6.83 (2.82)	7.37 (2.51)
Incidence (persons)	1871	1163
Total person-years	36,015.19	38,856.24
Cumulative incidence rate (per 1 000 person-years), mean (± SD)	51.95 (36.77–88.49)	29.93 (22.32–45.38)

The risk of type 2 diabetes increased both in the unadjusted and adjusted Cox regression models (adjusted HR = 1.47 [95% CI 1.3–1.67] for less than 2 years of exposure; 1.72 [1.51–1.96] for 2 to 5 years of exposure; and 1.85 [1.62–2.1] for over 5 years of exposure)

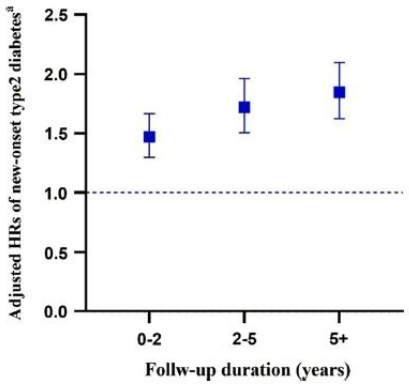
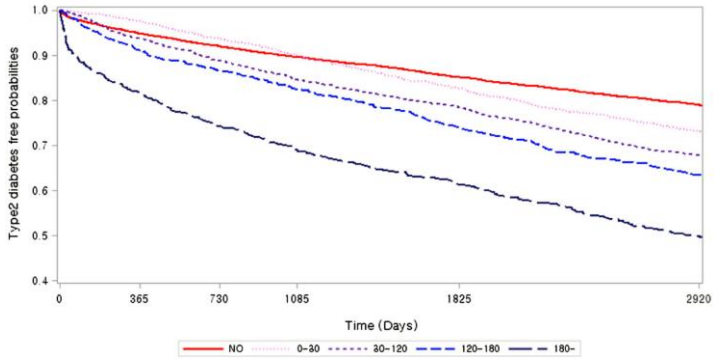


Fig.: Time-varying hazard ratios (95% CI) of statin use compared to non-statin use

The next model assessed whether the mean cumulative statin dosage per year was associated with the risk of new-onset type 2 diabetes. Patients with higher statin maintenance doses had a higher risk of new-onset type 2 diabetes. The risk of new-onset type 2 diabetes differed among statin users according to cDDD per year (adjusted HR = 1.31 [95% CI 1.18–1.46] for less than 30 cDDD per year; 1.58 [1.43–1.75] for 30–120 cDDD per year; 1.83 [1.62–2.08] for 120–180 cDDD per year; and 2.83 [2.51–3.19] for more than 180 cDDD per year (Fig.).



Kaplan-Meier curves according to cumulative daily defined dose (cDDD) per year

There is a dose–response relationship in terms of statin use duration and dose maintenance. Periodic screening and monitoring for incident type 2 diabetes may be warranted in long-term statin users.

The diabetogenic effect of pitavastatin was not statistically significant, but the risk was the largest for atorvastatin. Long-term exposure (≥ 5 years) to statins was associated with a statistically significant increase in the risk of new onset type 2 diabetes in all statin subtypes explored, with the highest magnitude for simvastatin (HR = 1.916, 95% CI 1.647–2.228) followed by atorvastatin (HR = 1.830, 95% CI 1.487–2.252). The current study confirms the need for rigorous monitoring of patients taking statins, particularly those with established risk factors for diabetes onset. Study findings also suggest the necessity of taking the diabetogenicity of statins into consideration in clinical practice, emphasizing the concomitant need for dietary control and exercise.

Source: Na, E., et al. Cardiovasc Diabetol 2020. 19(67) https://doi.org/10.1186/s12933-020-01037-0

Association between Glycemic control and diabetic foot ulcer outcomes: A meta-analysis

Nearly one-third of patients with diabetes will experience a diabetic foot ulcer (DFU) in their lifetime, typically in the setting of peripheral arterial disease (PAD), peripheral neuropathy, and trauma.

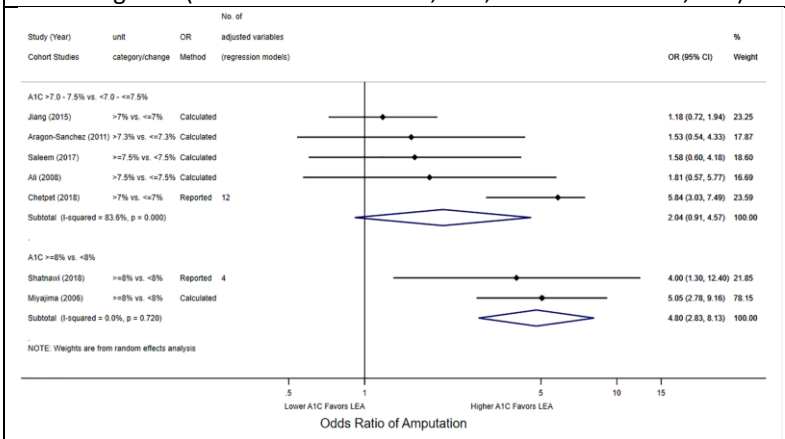
DFUs are associated with significant morbidity, including infection and lower extremity amputation (LEA), as well as increased risk of mortality. Previously published narrative reviews of observational studies have demonstrated that the association between glycemic control and wound outcomes among DFUs remains unclear. Given limited evidence on the topic, this study was conducted to evaluate the association between glycemic control (hemoglobin A1C, fasting glucose, and random glucose) and the outcomes of wound healing and lower extremity amputation (LEA)

among patients with diabetic foot ulcers (DFUs).

Medline, EMBASE, Cochrane Library, and Scopus were searched for observational studies published up to March 2019. Five independent reviewers assessed in duplicate the eligibility of each study based on predefined eligibility criteria and two independent reviewers assessed risk of bias. A meta-analysis was performed to calculate a pooled odd ratio (OR) or hazard ratio (HR) using random effects for glycemic measures in relation to the outcomes of wound healing and LEA. Subgroup analyses were conducted to explore potential source of heterogeneity between studies. The study protocol is registered with PROSPERO.

Of 4572 study records screened, 60 observational studies met the study eligibility criteria of which 47 studies had appropriate data for inclusion in one or more meta-analyses (n = 12,604 DFUs). For cohort studies comparing A1C >7.0 to 7.5% vs. lower A1C levels, the pooled OR for LEA was 2.04 (95% CI, 0.91, 4.57) and for studies comparing A1C ≥ 8% vs. <8%, the pooled OR for LEA was 4.80 (95% CI 2.83, 8.13). For cohort studies comparing fasting glucose ≥126 vs. <126 mg/dl, the pooled OR for LEA was 1.46 (95% CI, 1.02, 2.09).

Forest plot of cohort studies on the association between odds ratio (OR) of lower extremity amputation (LEA) as the outcome of interest stratified by studies using similar A1C categories (>7.0 to 7.5% vs. lower, n=5; and ≥ 8% vs. <8%, n=2).



HbA1C levels ≥8% and fasting glucose levels ≥126 mg/dl are associated with increased likelihood of LEA in patients with DFUs.

Study findings suggest that A1C levels of 8% or greater and fasting glucose levels of 126 mg/dl and greater are associated with increased likelihood of LEA in patients with existing DFUs, though the reasons for these associations cannot be ascertained from this study. Considering that many patients with DFUs have advanced diabetes-related complications, an A1C target of 7% to 8% is likely appropriate for most of these patients and aligns with general practice guidelines.

Source: Lane KL et al. J Diabetes Compl 2020. https://doi.org/10.1016/j.jdiacomp.2020.107638

Continuous Glucose Monitoring in Pregnancy: CONCEPTT trial

Maternal glucose is the major determinant of fetal growth, predicting large for gestational age (LGA) infants and neonatal outcomes. However, maternal glucose is dynamic, with glucose tolerance and insulin sensitivity varying across the 24-h day with a circadian rhythmicity. This study was conducted to determine if temporal glucose profiles differed between 1) women who were randomized to real-time continuous glucose monitoring (RT-CGM) or self-monitored blood glucose (SMBG), 2) women who used insulin pumps or multiple daily insulin injections (MDIs), and 3) women whose infants were born large for gestational age (LGA) or not, by assessing CGM data obtained from the Continuous Glucose Monitoring in Women With Type 1 Diabetes in Pregnancy Trial (CONCEPTT). Standard summary metrics and functional data analysis were applied to CGM data from the CONCEPTT trial (RT-CGM, n = 100; SMBG, n = 100) taken at baseline and at 24- and 34-weeks' gestation. Multivariable regression analysis determined if temporal differences in 24-h glucose profiles occurred between comparators in each of the three groups.

A: RT-CGM group to SMBG control group	Baseline		24 weeks		34 weeks	
	CGM	SMBG	CGM	SMBG	CGM	SMBG
Number	100	100	89	90	77	76
Glucose, mmol/L	7.3 ± 1.2	7.6 ± 1.1	7.6 ± 1.2	7.8 ± 1.3	6.7 ± 0.9	7.0 ± 1.1
0001–0600 h glucose, mmol/L	6.7 ± 1.5	7.1 ± 1.4	**7.2 ± 1.4**	**7.0 ± 1.4**	6.2 ± 1.0	6.3 ± 1.2
0601–0000 h glucose, mmol/L	7.5 ± 1.3	7.8 ± 1.2	**7.7 ± 1.3**	**8.1 ± 1.4**	7.0 ± 1.0	7.3 ± 1.2
Percentage of time 3.5–7.8 mmol/L	51.7 ± 13.0	51.5 ± 13.7	53.0 ± 15.5	49.8 ± 15.0	**67.6 ± 12.6**	**61.3 ± 15.5**
Percentage of time below 3.5 mmol/L	**10.0 ± 7.7**	**7.8 ± 6.4**	4.8 ± 4.8	5.5 ± 5.7	4.6 ± 4.9	5.7 ± 5.2
Percentage of time above 7.8 mmol/L	38.4 ± 14.9	40.6 ± 13.8	42.3 ± 17.6	44.7 ± 16.0	**27.9 ± 13.4**	**33.1 ± 15.0**
Individual SD	3.1 ± 0.8	3.2 ± 0.8	2.7 ± 0.6	2.9 ± 0.7	**2.2 ± 0.5**	**2.5 ± 0.7**
Individual CV, %	42.2 ± 8.7	42.4 ± 8.1	35.6 ± 5.9	36.9 ± 7.2	**32.5 ± 5.8**	**34.9 ± 7.6**

Functional data analysis of temporal glucose profiles gives important information about differences in glucose control.

Functional data analysis revealed that women using RT-CGM had significantly lower glucose (0.4–0.8 mmol/L [7–14 mg/dL]) for 7 h/day (0800 h to 1200 h and 1600 h to 1900 h) compared with those with SMBG. Women using pumps had significantly higher glucose (0.4–0.9 mmol/L [7–16 mg/dL]) for 12 h/day (0300 h to 0600 h, 1300 h to 1800 h, and 2030 h to 0030 h) at 24 weeks with no difference at 34 weeks compared with MDI. Women who had an LGA infant ran a significantly higher glucose by 0.4–0.7 mmol/L (7–13 mg/dL) for 4.5 h/day at baseline, by 0.4–0.9 mmol/L (7–16 mg/dL) for 16 h/day at 24 weeks, and by 0.4–0.7 mmol/L (7–13 mg/dL) for 14 h/day at 34 weeks. Figure illustrates the difference in CGM glucose across the 24-h day in women who were randomized to RT-CGM compared with SMBG after applying FDA. Women who used RT-CGM ran a significantly lower glucose by 0.4–0.8 mmol/L (7–14 mg/dL) for 7 h during the daytime (0800 h to 1200 h and 1600 h to 1900 h).

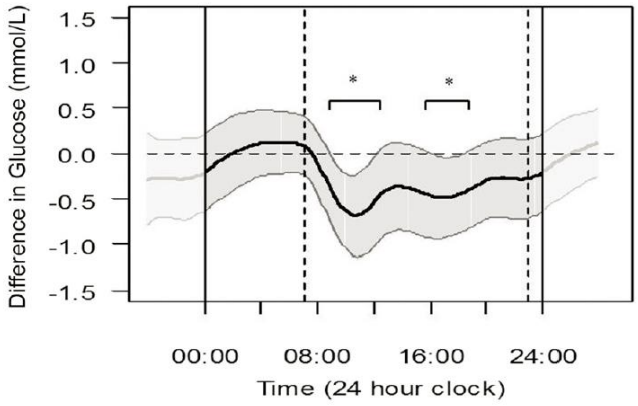


Figure 1—Differences in mean temporal glucose levels across the 24-h day, assessed by FDA (at 24 and 34 weeks' gestation combined) between those women who were randomized to RT-CGM (represented by the dark wavy line) compared with those using SMBG (represented by the horizontal zero dotted line) with 95% pointwise CIs (gray section). Where both of the CIs sit to the same side of 0.0, there is a significant difference. Dashed vertical lines represent daytime at 0700 h and 2300 h. *Significant differences using 95% CIs.

Functional data analysis of temporal glucose profiles gives important information about differences in glucose control and its timing, which are undetectable by standard summary metrics. Women using RT-CGM were able to achieve better daytime glucose control, reducing fetal exposure to maternal glucose.

Source: Scott EM et al. Diabetes Care. 2020 Jun;43(6):1178-1184. doi: 10.2337/dc19-2527.