MICRO LABS LIMITED

Diabetes Update

Vol. 1 | Issue 7 | 2020

Dear Doctor,

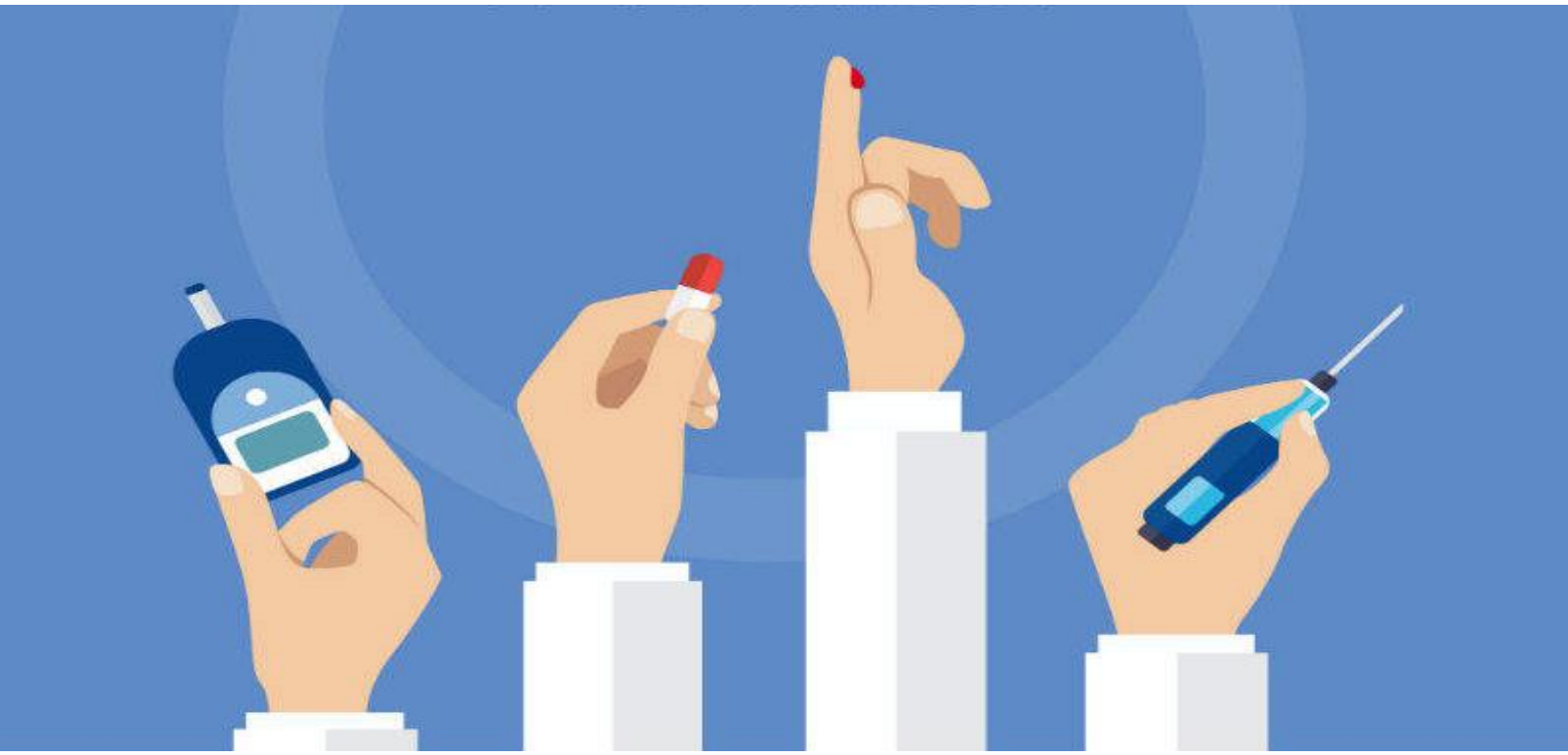
Greetings from Micro Labs Limited. We are happy to bring you "DIABETES UPDATE" which contains latest and interesting news in the field of Diabetes and Endocrinology.

- Tolimidone : A Novel non-PPAR gamma Insulin Sensitiser
- Switching from Neutral Protamine Hagedorn Insulin to Insulin Glargine 300U/mL
- Association between Major depressive disorder and cardio-metabolic diseases

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



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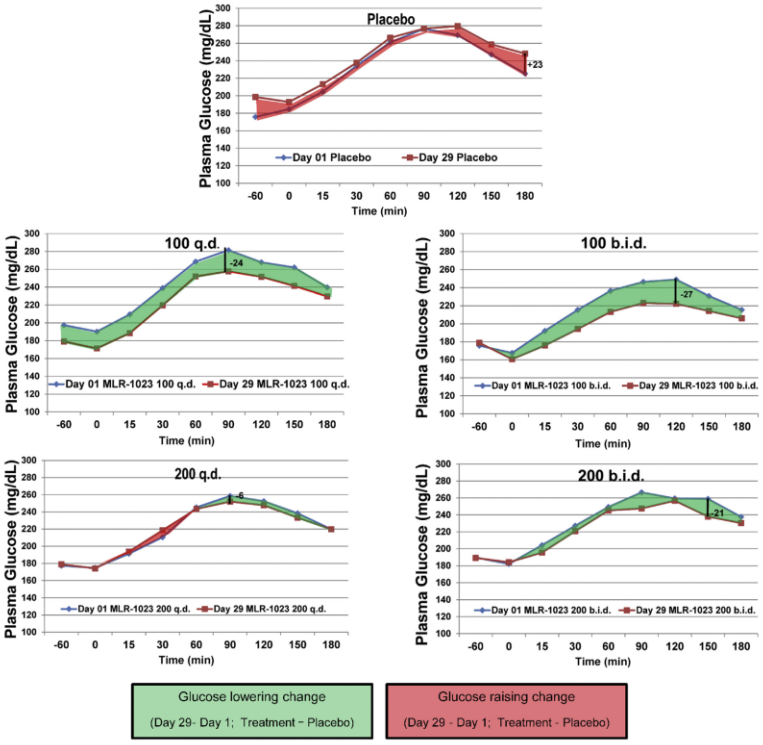
Tolimidone : A Novel non-PPAR gamma Insulin Sensitizer

Insulin Sensitizer Tolimidone (MLR-1023) was initially unsuccessfully was developed for gastric ulcer disease. is a novel insulin sensitizer that does not activate the PPAR pathways and may provide a potentially important treatment advance in attempts to reverse the underlying cause of type 2 diabetes without promoting weight gain. This was a randomized, double-blind, five-group, parallel-arm, phase 2, dose-finding trial. Patients were randomly assigned, using an interactive voice/web response system, to one of five treatment groups to receive 2 daily tablets containing either Tolimidone (100-mg BID or 200-mg, once-daily OD) or placebo for 28 days.



The primary endpoint was postprandial glucose (PPG) area under the curve (AUC0–3h) in a mixed meal tolerance test (MMTT) at day 29. Secondary endpoints included changes in fasting plasma glucose (FPG), insulin, HbA1c, lipids and body weight and adverse events.

The placebo-corrected least-squares mean differences (ΔLSM) in MMTT PPG AUC0-3 h (mmol/L) were −5.96 and −5.6 (both p = 0.03) in the MLR-1023 100-mg qd and 100-mg bid groups, respectively. The placebo-corrected ΔLSMin FPG (mmol/L)was−2.34 (p=0.003) in the MLR-1023 100-mg qd group. Triglycerides improved with MLR-1023 (ΔLSM, −0.56 mmol/L,

Tolimidone may offer benefits in terms of not only postprandial glycemic levels but also improved lipid profiles with weight neutral effects.

p=0.07 and −0.59 mmol/L, p = 0.05) in the 200mg qd and 200 mg bid groups, respectively. Reductions in fasting insulin, HbA1c and body weight were not statistically significant. Most common adverse events with MLR-1023 treatment were headache (4.2%) and somnolence (2.5%).

Increasing worldwide prevalence of type 2 diabetes and the suboptimal efficacy of existing treatments emphasizes the need for antidiabetic agents with improved benefit-risk profiles. Results from this study also indicate that Tolimidone may offer benefits in terms of not only postprandial glycemic levels but also improved lipid profiles with weight neutral effects.

Source: Lee MK et al. J Diabetes Complications. 2020;34(5):107555. doi:10.1016/j.jdiacomp.2020.107555

Switching from Neutral Protamine Hagedorn Insulin to Insulin Glargine 300U/mL

Type 2 diabetes mellitus (T2DM) is a major cause of morbidity and mortality worldwide and is an important public health issue. A significant proportion of insulin-treated patients with T2DM do not reach target glycated haemoglobin (HbA1c) values, which ultimately increases their risk of long-term microvascular and macrovascular complications. One potential option to improve diabetes control in these patients may be the use of new insulin formulations including second-generation basal insulin analogues such as insulin glargine 300 U/mL (Gla-300). Several published randomised controlled trials have assessed the clinical effectiveness of Gla-300, mostly versus insulin glargine 100 U/mL as well as insulin degludec. However, there is limited information about the real-world effectiveness of Gla-300 when patients are transitioned directly

from neutral protamine Hagedorn (NPH) human basal insulin. The primary objective of this study was to evaluate the effectiveness of Gla-300, defined as the percentage of participants with an HbA1c reduction of ≥0.5%, 6 months after switching from NPH insulin, in participants with T2DM. Secondary objectives included the safety assessment based on the percentage of patients experiencing ≥1 episodes and the number of hypoglycaemic episodes by category: severe, symptomatic, symptomatic confirmed, diurnal or nocturnal, change in body weight, and insulin dose. A total of 469 participants completed the 6-month observation period.

Mean baseline HbA1c was 9.19%. The percentage of participants with a ≥0.5% improvement in HbA1c from baseline was 71.7% at 6 months. Mean HbA1c decreased at 3 and 6 months by 0.77% (±0.98) and 1.01% (±1.12), respectively (p < 0:00001 versus baseline), while fasting glycaemia decreased by 32 mg/dL and 37 mg/dL, respectively (p < 0:00001 versus baseline). There were moderate increases in the doses of both Gla-300 and, if used, short-acting insulins during the 6 months of observation. The percentage of participants with ≥1 hypoglycaemia event during the preceding 4 weeks decreased significantly from baseline to 3 and 6 months, as did the proportion with symptomatic hypoglycaemia at night (p < 0:00001 versus baseline). No participants had severe hypoglycaemia after a switch to Gla-300. Body mass, waist and hip circumferences, and waist : hip ratio did not change significantly. In conclusion, this large, prospective, observational study demonstrated that switching from NPH insulin to Gla-300 resulted in a significant improvement in HbA1c, with only a moderate increase in insulin dose, a decreased risk of hypoglycaemia, and no increase in body weight.

Switching from NPH insulin to Gla-300 resulted in a significant improvement in HbA1c.

Source: Wolnik B et al. J Diabet Res 2020, ID 8751348: 1-8.

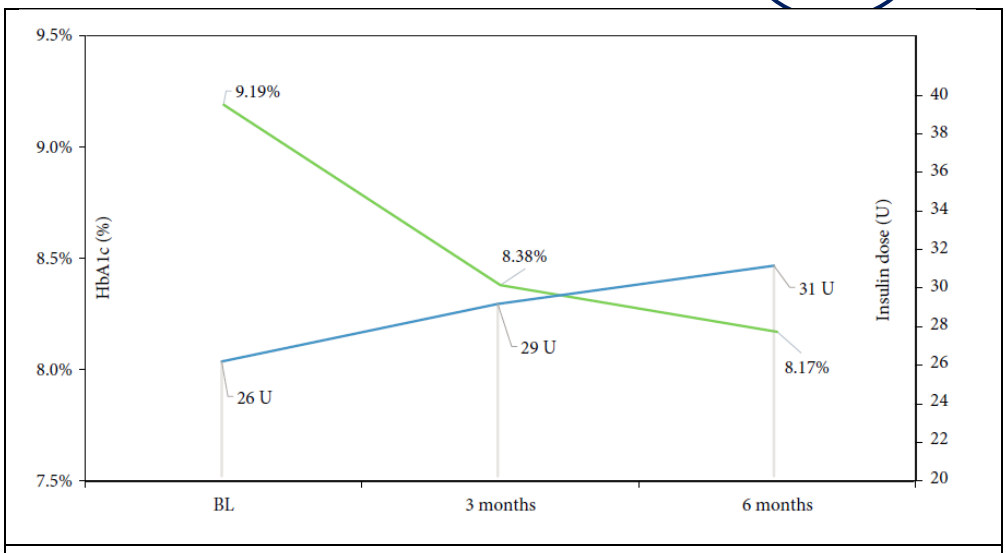
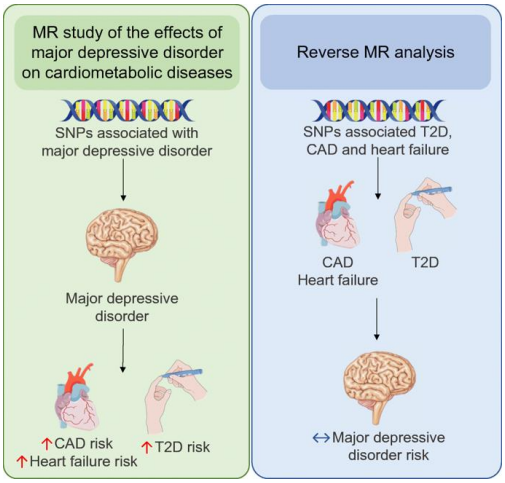


Figure : Relative changes in HbA1c versus Gla-300 dose in the study population.
Blue line: glargine 300 doses at baseline, 3 months, and 6 months. Green line: HbA1c values at baseline, 3 months, and 6 months

Association between Major depressive disorder and cardio-metabolic diseases

Type 2 diabetes and Major depressive disorder (MDD) are both important health issues across the globe. Observational studies have shown a bidirectional association between major depressive disorder (MDD) and cardiometabolic diseases. Tang et al. conducted a two-sample bidirectional Mendelian randomisation (MR) study to assess the causal associations of MDD with type 2 diabetes, coronary artery disease (CAD) and heart failure and vice versa.



Tang et al. extracted summary-level data for MDD, type 2 diabetes, CAD and heart failure from corresponding published large

genome-wide association studies of individuals mainly of European-descent. In total, 96 SNPs for MDD, 202 SNPs for type 2 diabetes, 44 SNPs for CAD and 12 SNPs for heart failure were proposed as instrumental variables at the genome-wide significance level ($p < 5 \times 10-8$). The random-effects inverse-variance weighted method was used for the main analyses.

Genetic liability to MDD was significantly associated with type 2 diabetes and CAD at the Bonferroni-corrected significance level. The ORs of type 2 diabetes and CAD were respectively 1.26 (95% CI 1.10, 1.43; $p = 6 \times 10-4$) and 1.16 (95% CI 1.05, 1.29; $p = 0.0047$) per one-unit increase in loge odds of MDD. There was a suggestive association between MDD and heart failure (OR 1.11 [95% CI 1.01, 1.21]; $p = 0.033$). We found limited evidence supporting causal effects of cardiometabolic diseases on MDD risk in the reverse MR analyses. The present study strengthened the evidence that MDD is a potential risk factor for type 2 diabetes and CAD. Whether MDD is causally related to heart failure needs further study.

Source: Tang B, et al. Diabetologia. 2020;10.1007/s00125-020-05131-6

MDD is a potential risk factor for type 2 diabetes and CAD