MICRO LABS LIMITED

Diabetes Update

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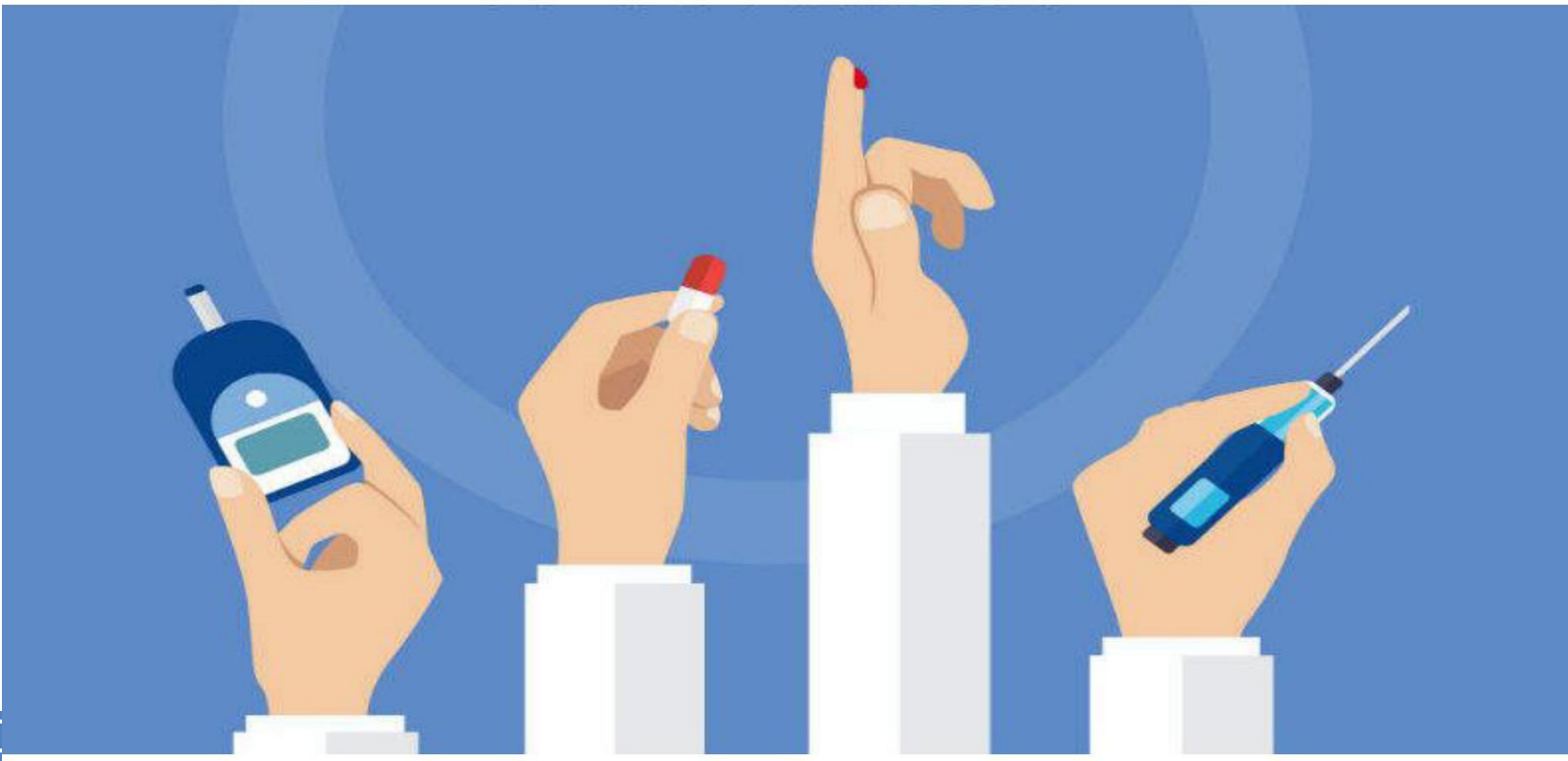
Dear Doctor,

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.

- **Relative Hypoxia and Early Diabetic Kidney Disease in Type 1 Diabetes**
- **Intakes of Vitamin B levels in Relation to Diabetes Incidence Among Young Adults: A 30-Year Follow-up CARDIA Study**
- **Cost-effectiveness of a Stepwise Approach vs Standard Care for Diabetes Prevention in India**

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

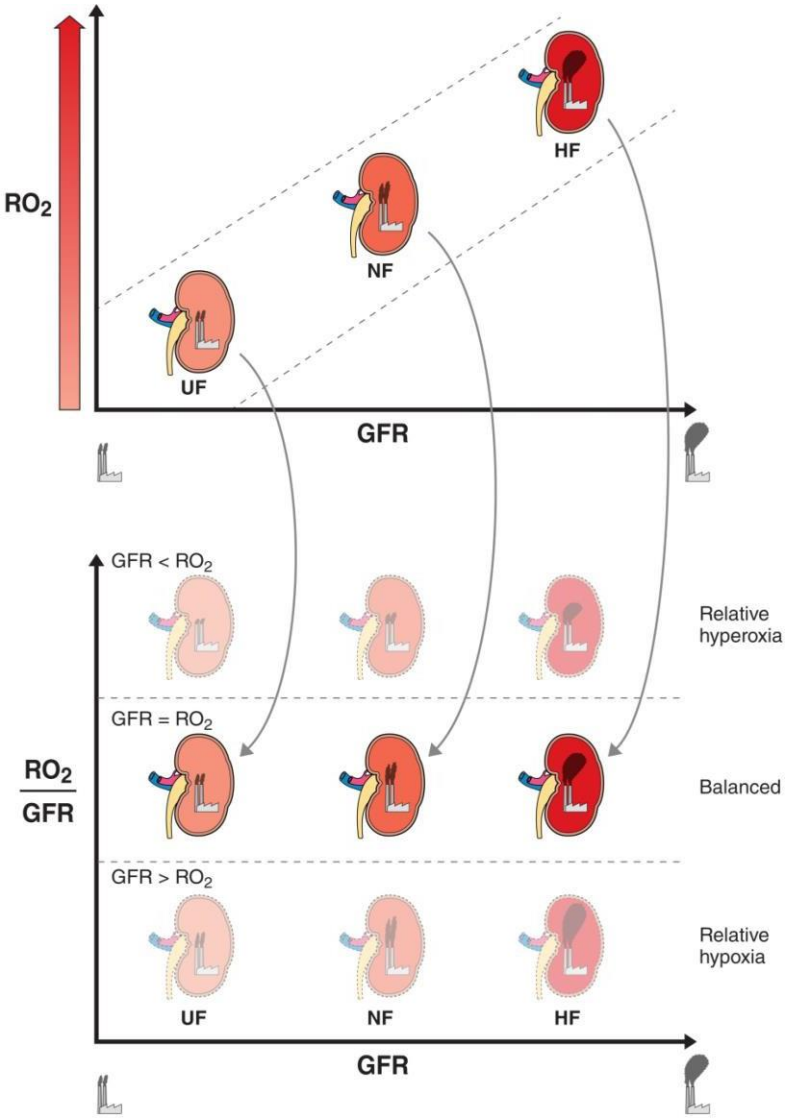


Relative Hypoxia and Early Diabetic Kidney Disease in Type 1 Diabetes

Almost 30% of people with type 1 diabetes (T1D) will develop diabetic kidney disease (DKD). Current treatments, such as control of hyperglycemia and hypertension, are beneficial, but only partially protect against DKD. Finding new, safe and effective therapies to halt early DKD progression in T1D has proven to be challenging as demonstrated by the outcomes from the recent Adolescent Type 1 Diabetes Cardio-Renal Intervention Trial (AdDIT) of ACE inhibitors and the adult Preventing Early Renal Loss in Diabetes (PERL) trials of uric acid lowering

The objective of this study was to compare the ratio of renal oxygen availability (RO2) to GFR (RO2:GFR), a measure of relative renal hypoxia, in adolescents with and without type 1 diabetes (T1D) and relate the ratio to albuminuria, renal plasma flow (RPF), fat mass, and insulin sensitivity (M/I). RO2 was estimated by blood oxygenation level dependent (BOLD) MRI, fat mass by DXA, GFR and RPF by iohexol and p-aminohippurate clearance, albuminuria by urine albumin-to-creatinine ratio (UACR), and M/I from steady-state glucose infusion rate/insulin (mg/kg/min) by hyperglycemic clamp in 50 adolescents with T1D (16.1±3.0 years, HbA1c 8.6±1.2%) and 20 controls of similar BMI (16.1±2.9 years, HbA1c 5.2±0.2%). The RO2:GFR (ms/ml/min) was calculated as renal oxygen availability (T2*, ms) divided by GFR (ml/min). Whole-kidney RO2:GFR was 25% lower in adolescents with T1D vs. controls ($p<0.0001$). In adolescents with T1D, lower whole-kidney RO2:GFR associated with higher UACR ($r=-0.31$, $p=0.03$), RPF ($r=-0.52$, $p=0.0009$) and fat mass ($r=-0.33$,

p=0.02). Lower medullary RO2:GFR associated with lower M/I (r=0.31, p=0.03).



RO2:GFR and Relative Renal Hypoxia

The top figure above illustrates the relationship between kidney oxygen availability (RO2) and glomerular filtration rate (GFR). A high GFR (workload) requires a high kidney oxygen availability to sustain the high energy expenditure. Therefore, whole-kidney hyperfiltration (HF) requires higher kidney oxygen availability compared to normofiltration (NF) and underfiltration (UF). The height of the smokestack plumes represents the magnitude of GFR. The bottom figure illustrates the ratio between kidney oxygen availabilit (RO2) and GFR across UF, NF and HF. Additionally, the bottom figure demonstrates 3 energetic scenarios (relative hyperoxia [RO2>GFR], balance [RO2=GFR] and relative hypoxia [RO2<GFR]) across the stages of diabetic kidney disease

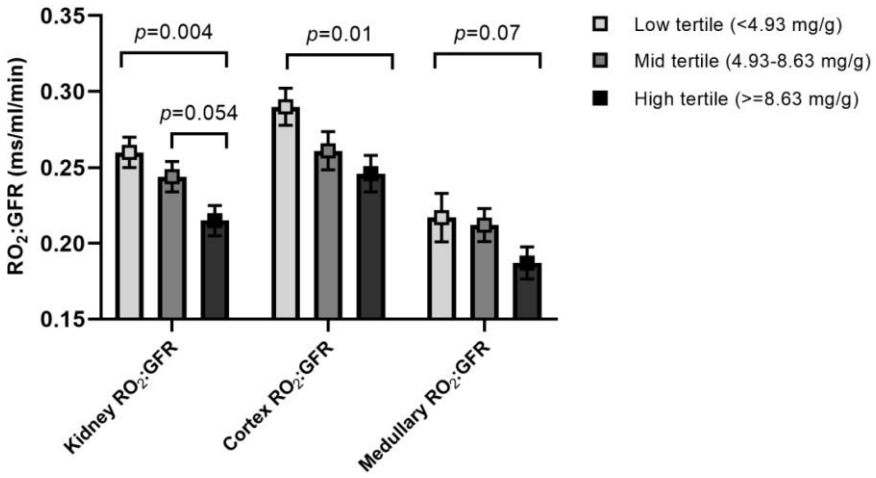


Figure 2. RO2:GFR across Tertiles of UACR
Kidney RO2:GFR, cortex RO2:GFR, and medullary RO2:GFR across tertiles of UACR. Data presented are adjusted means (least square means) and standard errors. Models are adjusted for age, sex and HbA1c.

Adolescents with T1D exhibited relative renal hypoxia that associated with albuminuria, increased RPF, fat mass, and insulin resistance. These data suggest a potential role of renal hypoxia in the development of DKD.

Source: Vinovskis C et al. Diabetes 2020 Jul; db200457. https://doi.org/10.2337/db20-0457

Intakes of Vitamin B levels in Relation to Diabetes Incidence Among Young Adults: A 30-Year Follow-up CARDIA Study

The high prevalence of type 2 diabetes mellitus (T2DM) is a severe public health concern worldwide. Hyperhomocysteinemia has emerged as a risk factor for T2DM due to its association with insulin resistance (IR). Hyperhomocysteinemia may be caused by genetic defects, renal dysfunction, or dietary factors, including low intakes of folate, vitamin B6, and B12. These B vitamins play a pivotal role in homocysteine (Hcy) degradation by acting as a prerequisite substrate donor (folate) or as essential coenzymes (vitamin B6 and B12). Additionally, these B vitamins are vital components of one-carbon metabolism that contributes to DNA methylation, which is critical for the pathogenesis of diabetes. The study was conducted to prospectively examine intakes of folate, vitamin B6, and vitamin B12 in relation to diabetes incidence in a large U.S. cohort.

A total of 4,704 American adults aged 18–30 years and without diabetes were enrolled in 1985–1986 and monitored until 2015–2016 in the Coronary Artery Risk Development in Young Adults (CARDIA) study. Dietary assessment was conducted by a validated dietary-history questionnaire at baseline, in 1992–1993, and in 2005–2006. The cumulative average intakes of folate, vitamin B6, and vitamin B12 were used in the analyses. Incident diabetes was ascertained by plasma glucose levels, oral glucose tolerance tests, hemoglobin A1c concentrations, and/or antidiabetic medications.

During 30 years (mean 20.5 ± 8.9) of follow-up, 655 incident cases of diabetes occurred. Intake of folate, but not vitamin B6 or vitamin B12,

was inversely associated with diabetes incidence after adjustment for potential confounders. Compared with the lowest quintile of total folate intake, the multivariable-adjusted hazard ratios (95% CI) in quintile 2–5 were 0.85 (0.67–1.08), 0.78 (0.60–1.02), 0.82 (0.62–1.09), and 0.70 (0.51–0.97; Ptrend = 0.02). Higher folate intake was also associated with lower plasma homocysteine (Ptrend < 0.01) and insulin (Ptrend < 0.01). Among supplement users, folate intake was inversely associated with serum C-reactive protein levels (Ptrend < 0.01). Intake of folate in young adulthood was inversely associated with diabetes incidence in midlife among Americans. The observed association may be partially explained by mechanisms related to homocysteine level, insulin sensitivity, and systemic inflammation.

	Quintiles of nutrient intake					
	Q1	Q2	Q3	Q4	Q5	P_{trend}
Folate (n = 4,703)						
Range (μg/day)	<281.6	281.6–393.4	393.4–508.4	508.4–693.5	≥693.5	NA
Median (μg/day)	216.4	338.9	450.0	591.2	885.7	NA
No. of cases/participants	147/940	150/941	125/941	132/941	101/940	NA
Model 1	1 [Ref.]	0.80 (0.63, 1.01)	0.66 (0.52, 0.86)	0.66 (0.51, 0.86)	0.48 (0.36, 0.64)	<0.01
Model 2	1 [Ref.]	0.93 (0.74, 1.18)	0.81 (0.63, 1.05)	0.84 (0.64, 1.09)	0.68 (0.50, 0.92)	<0.01
Model 3 (final model)	1 [Ref.]	0.85 (0.67, 1.08)	0.78 (0.60, 1.02)	0.82 (0.62, 1.09)	0.70 (0.51, 0.97)	0.02
B_6 (n = 3,894)						
Range (mg/day)	<1.7	1.7–2.4	2.4–3.2	3.2–4.6	≥4.6	NA
Median (mg/day)	1.4	2.0	2.7	3.8	6.8	NA
No. of cases/participants	143/779	112/777	123/779	111/779	98/780	NA
Model 1	1 [Ref.]	0.74 (0.58, 0.96)	0.84 (0.65, 1.09)	0.75 (0.57, 0.99)	0.64 (0.48, 0.85)	0.06
Model 2	1 [Ref.]	0.86 (0.66, 1.10)	0.96 (0.74, 1.25)	0.94 (0.71, 1.24)	0.82 (0.61, 1.11)	0.69
Model 3 (final model)	1 [Ref.]	0.89 (0.68, 1.15)	1.07 (0.80, 1.42)	1.06 (0.76, 1.47)	1.04 (0.71, 1.51)	0.40
B_{12} (n = 3,894)						
Range (μg/day)	<4.1	4.1–6.1	6.1–8.7	8.7–13.8	≥13.8	NA
Median (μg/day)	3.0	5.1	7.3	10.6	21.0	NA
No. of cases/participants	120/778	131/779	121/780	104/778	111/779	NA
Model 1	1 [Ref.]	1.05 (0.82, 1.35)	0.96 (0.74, 1.25)	0.86 (0.65, 1.14)	0.88 (0.66, 1.16)	0.49
Model 2	1 [Ref.]	1.08 (0.84, 1.39)	1.02 (0.79, 1.34)	0.99 (0.75, 1.31)	1.08 (0.81, 1.44)	0.46
Model 3 (final model)	1 [Ref.]	1.04 (0.80, 1.35)	1.08 (0.81, 1.44)	1.14 (0.83, 1.56)	1.29 (0.91, 1.84)	0.053

Multivariable-adjusted HRs (95% CIs) of incident diabetes by quintiles of B vitamin intake levels: the CARDIA study,

This longitudinal cohort study monitored over 30 years suggest that American young adults with higher folate intake are less likely to develop diabetes later in life, presumably through mechanisms related to Hcy level, IR and systemic inflammation

Source: Zhu J et al. Diabetes Care 2020 Jul; dc200828. https://doi.org/10.2337/dc20-0828

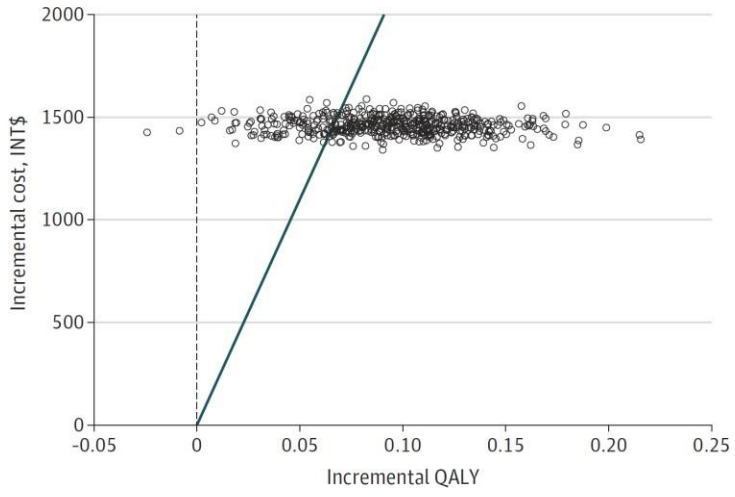
Cost-effectiveness of a Stepwise Approach vs Standard Care for Diabetes Prevention in India

A stepwise approach that includes screening and lifestyle modification followed by the addition of metformin for individuals with high risk of diabetes is recommended to delay progression to diabetes; however, there is scant evidence regarding whether this approach is cost-effective. This study was done to estimate the cost- effectiveness of a stepwise approach in the Diabetes Community Lifestyle Improvement Program.

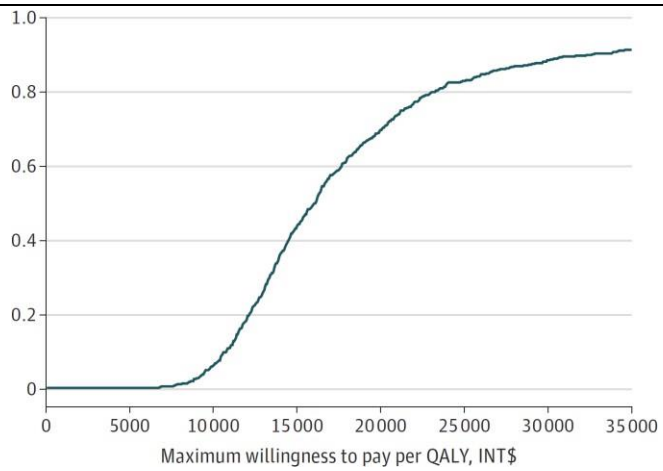
This economic evaluation study included 578 adults with impaired glucose tolerance, impaired fasting glucose, or both. Participants were enrolled in the Diabetes Community Lifestyle Improvement Program, a randomized clinical trial with 3-year follow-up conducted at a diabetes care and research center in Chennai, India. The intervention group underwent a 6-month lifestyle modification curriculum plus stepwise addition of metformin; the control group received standard lifestyle advice. Cost, health benefits, and incremental cost-

effectiveness ratios (ICERs) were estimated from multipayer (including direct medical costs) and societal (including direct medical and nonmedical costs) perspectives. Costs and ICERs were reported in 2019 Indian rupees (INR) and purchasing power parity–adjusted international dollars (INT $).

The mean (SD) age of the 578 participants was 44.4 (9.3) years, and 364 (63.2%) were men. Mean (SD) body mass index was 27.9 (3.7), and the mean (SD) glycated hemoglobin level was 6.0% (0.5). Implementing lifestyle modification and metformin was associated with INR 10 549 (95% CI, INR 10 134-10 964) (INT $803 [95% CI, INT $771-834]) higher direct costs; INR 5194 (95% CI, INR 3187-INR 7201) (INT $395; 95% CI, INT $65-147) higher direct nonmedical costs, an absolute diabetes risk reduction of 10.2% (95% CI, 1.9% to 18.5%), and an incremental gain of 0.099 (95% CI, 0.018 to 0.179) quality-adjusted life-years per participant.



Cost-effectiveness plane of incremental costs and incremental QALYs with screening costs



Cost-effectiveness acceptability curve showing the probability of D-CLIP intervention being cost-effective for QALYs with screening costs included

From a multipayer perspective (including screening costs), mean ICERs were INR 1912 (INT $145) per 1 percentage point diabetes risk reduction, INR 191 090 (INT $14 539) per diabetes case prevented and/or delayed, and INR 196 960 (INT $14 986) per quality-adjusted life-year gained. In the scenario of a 50% increase or decrease in screening and intervention costs, the mean ICERs varied from INR 855 (INT $65) to INR 2968 (INT $226) per 1 percentage point diabetes risk reduction, from INR 85 495 (INT $6505) to INR 296 681 (INT $22 574) per diabetes case prevented, and from INR 88 121 (INT $6705) to INR 305 798 (INT $23 267) per quality-adjusted life-year gained. The findings of this study suggest that a stepwise approach for diabetes prevention is likely to be cost-effective, even if screening costs for identifying high-risk individuals are added.

Source: Islek D et al. JAMA Netw Open. 2020;3(7):e207539. doi:10.1001/jamanetworkopen.2020.7539.