Study of Lipid Profile, Atherogenic Index and Insulin Resistance in Patients with Type 2 Diabetes Mellitus

Shrewastwa MK[1], BK SK[2], Karn SL[3]

ABSTRACT

Introduction: Type 2 diabetes mellitus is a major metabolic disorder associated with dyslipidemia, insulin resistance, and increased cardiovascular risk. Alterations in lipid metabolism contribute significantly to the progression of atherosclerosis. **Aims:** To evaluate lipid profiles, atherogenic indices, and insulin resistance in patients with Type 2 diabetes and compare them with non-diabetic controls. **Methods:** A hospital based comparative cross-sectional study was conducted among 120 type 2 diabetes patients and 120 age-matched controls. Fasting glucose, insulin, glycated hemoglobin, and lipid parameters were measured. Atherogenic indices including Cardiac Risk Ratio, Atherogenic Coefficient, and Atherogenic Index of Plasma were calculated. Insulin resistance was assessed using the Homeostasis Model Assessment of Insulin Resistance. **Results:** Type 2 diabetes patients exhibited significantly higher triglycerides, total cholesterol, Low density lipoprotein, and atherogenic indices, while High density lipoprotein was reduced compared to controls. Homeostasis Model Assessment of Insulin Resistance values were markedly elevated in diabetics compared to control. (4.82 ± 1.56 vs. 2.12 ± 0.84, $p < 0.001$). Correlation analysis revealed strong positive associations between Homeostasis Model Assessment of Insulin Resistance and triglycerides, low density lipoprotein, cardiac risk ratio, Atherogenic Coefficient, and Atherogenic Index of Plasma, with Atherogenic Index of Plasma showing the strongest correlation ($r = 0.612$, $p < 0.001$). **Conclusion:** Patients with type 2 diabetes demonstrate significant dyslipidemia, elevated atherogenic indices, and increased insulin resistance. Atherogenic index of plasma emerged as a reliable marker of cardiovascular risk, highlighting the importance of routine evaluation of lipid profiles and atherogenic indices for early detection and prevention of cardiovascular complications in type 2 diabetes.

***Keywords*:** Atherogenic indices; Cardiovascular risk; Dyslipidemia; HOMA-IR; Insulin resistance; Type 2 diabetes mellitus

Authors:

1. Dr. Mukesh Kumar Shrewastwa
2. Dr. Shyam Kumar BK
3. Dr. Subhash Lal Karn

[1]Department of Biochemistry, Nepalgunj Medical College, Kohalpur, Banke, Nepal

[2]Department of Medicine, Nepalgunj Medical College, Kohalpur, Banke, Nepal

[3]Department of Microbiology, Nepalgunj Medical College, Kohalpur, Banke, Nepal

Address for Correspondence:

Dr. Mukesh Kumar Shrewastwa
Assistant Professor
Department of Biochemistry
Nepalgunj Medical College and Teaching Hospital
Kohalpur, Banke, Nepal
Email: mshrewastwa55@gmail.com

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a chronic metabolic disorder characterized by persistent hyperglycemia due to insulin resistance and impaired insulin secretion.[1,2] Its global prevalence has risen dramatically in recent decades, representing a major public health challenge with significant socioeconomic and healthcare consequences.[3,4] In developing countries such as Nepal, the burden of diabetes is increasing rapidly, driven by urbanization, sedentary lifestyles, and dietary transitions.[5] Dyslipidemia is a frequent metabolic abnormality in T2DM, typically presenting as elevated triglycerides, increased low-density lipoprotein cholesterol (LDL-C), and reduced high-density lipoprotein cholesterol (HDL-C).[6] These lipid disturbances contribute to the formation of atherogenic lipoproteins and accelerate the progression of cardiovascular disease (CVD), which remains the leading cause of morbidity and mortality among diabetic patients.[7] Insulin resistance plays a central role in this process by promoting free fatty acid release, altering hepatic lipid metabolism, and impairing lipoprotein clearance.[8] To improve cardiovascular risk assessment, composite measures such as atherogenic indices have been developed. The Atherogenic Index of Plasma (AIP), Cardiac Risk Ratio (CRR), and Atherogenic Coefficient (AC) provide integrated evaluations of lipid-related risk and are considered superior predictors compared to isolated

lipid parameters.[9,10] Insulin resistance can be quantified using the Homeostasis Model Assessment of Insulin Resistance (HOMA-IR), a widely accepted surrogate marker of impaired insulin sensitivity.[11] Understanding the interplay between dyslipidemia, atherogenic indices, and insulin resistance is crucial for early detection of cardiovascular risk in T2DM. This study was therefore undertaken to evaluate lipid profiles, calculate atherogenic indices, and examine their association with insulin resistance in patients with T2DM compared to non-diabetic controls.

METHODS

This investigation was designed as a hospital based comparative cross-sectional study conducted in the Department of Biochemistry at Nepalgunj Medical College and Teaching Hospital, Kohalpur, Nepal, between September 2024 and August 2025. Cross-sectional studies are widely employed in epidemiology to evaluate associations between exposures and outcomes at a single point in time, providing valuable insights into disease prevalence and metabolic alterations (dyslipidemia, insulin resistance, altered glucose metabolism in T2DM patients) in defined populations (Levin, 2006).[12]

Sample Size Determination

The sample size was calculated using the standard formula for prevalence-based cross-sectional studies:

$n=Z^2pq\ /d^2$, where (n) is the required sample size, (Z) is the standard normal deviate at a 95% confidence interval (1.96), (p) is the estimated prevalence of T2DM in Nepal (8.5%)[13], (q = 1 - p), and (d) is the allowable margin of error (5%).

$n= (1.96)^2\times0.085\times0.915/ (0.05)^2 =119.51$

The calculated sample size was approximately 120 participants per group, ensuring adequate statistical power. Thus, a total of 240 participants were enrolled, comprising 120 confirmed T2DM patients and 120 apparently healthy, age-matched controls.

Study Population

The control group consisted of apparently healthy, age- and sex-matched individuals recruited from hospital staff attendants and the local community. Controls had no history of diabetes mellitus or other metabolic disorders, including dyslipidemia, hypertension, thyroid disease, hepatic disease, or renal disease. They had normal fasting plasma glucose levels and were not receiving antidiabetic, lipid-lowering, or other medications known to affect glucose or lipid metabolism. Participants with T2DM were recruited through convenient sampling from patients attending the medicine outpatient department during the study period. Both newly diagnosed and previously diagnosed patients with T2DM attending the medicine outpatient department were included, provided they fulfilled the ADA diagnostic criteria and met the study eligibility criteria. Diagnosis of T2DM was based on the American Diabetes Association (ADA) diagnostic criteria and confirmed from patients' medical records and/or documented fasting plasma glucose values. A 75-g oral glucose tolerance test was not routinely performed in all participants. Diagnosis of diabetes was established according to the American Diabetes Association (ADA) criteria, which define diabetes as fasting plasma glucose (FPG) ≥126 mg/dL or 2-hour plasma glucose (2hPG) ≥200 mg/dL following a 75 g oral glucose tolerance test.[1]

Inclusion criteria consisted of adults aged 30–70 years with confirmed T2DM who provided written informed consent. Exclusion criteria included individuals with known hepatic, renal, or thyroid disorders; familial or genetic lipid disorders; pregnancy; or those receiving lipid-modifying medications other than routine antidiabetic therapy. These criteria were established to minimize confounding factors that could independently influence lipid metabolism and insulin sensitivity.

Ethical Considerations

Ethical approval was obtained from the Institutional Review Committee of Nepalgunj Medical College (IRC Ref. No. 11/081–082). Written informed consent was secured from all participants prior to enrollment.

Data Collection and Anthropometric Measurements

Demographic and anthropometric data were collected using standardized protocols. Age and sex were recorded, while height, weight, and waist circumference were measured using calibrated instruments. Body mass index (BMI) was calculated as weight (kg) divided by height squared (m^2).

$BMI=weight\ (kg) / height\ (m)^2$

Biochemical Analysis

Venous blood samples were collected after an overnight fast of 8–12 hours under aseptic conditions. Fasting plasma glucose was measured using enzymatic methods on a fully automated biochemistry analyzer (BS430). Serum lipid parameters including triglycerides (TG), total cholesterol (TC), HDL-C, and LDL-C were analyzed using enzymatic colorimetric assays on a fully automated biochemistry analyzer (BS430). Fasting serum insulin was measured using a fully automated immunoassay system (Maglumi 1200), while glycated hemoglobin (HbA1c) was determined by high-performance liquid chromatography (HPLC), the gold standard for HbA1c measurement.[14]

Calculation of Atherogenic Indices

Atherogenic indices were calculated using established formulas:

- Cardiac Risk Ratio (CRR): TC/HDL-C 10
- Atherogenic Coefficient (AC): (TC − HDL-C)/HDL-C
- Atherogenic Index of Plasma (AIP): log (TG/HDL-C) [9]

These indices provide integrated measures of lipid-related cardiovascular risk, offering superior predictive value compared to isolated lipid parameters.

Assessment of Insulin Resistance

Insulin resistance was evaluated using the Homeostasis Model Assessment of Insulin Resistance (HOMA-IR), calculated as:

HOMA-IR= Fasting Insulin (µIU/mL) × Fasting Glucose (mmol/L)/22.5

= Fasting insulin (µIU/mL) × Fasting plasma glucose (mg/dl)/405

This model, originally described by Matthews et al (1985)[15], remains a widely accepted surrogate marker for insulin sensitivity in both clinical and research settings.

Statistical Analysis

Data were analyzed using appropriate statistical software. Continuous variables were expressed as mean ± standard deviation (SD). Comparisons between T2DM patients and controls were performed using the independent Student's t-test. Pearson correlation analysis was applied to assess associations between lipid parameters, atherogenic indices, and HOMA-IR values. A p-value <0.05 was considered statistically significant.

RESULTS

Parameter	T2DM Patients (n=120)	Controls (n=120)	p-value
Age (years)	54.3 ± 9.2	52.7 ± 8.8	>0.05
BMI (kg/m²)	27.6 ± 3.4	24.2 ± 2.9	<0.05
Fasting glucose (mg/dL)	162.4 ± 38.5	89.3 ± 10.2	<0.001
HbA1c (%)	8.1 ± 1.3	5.2 ± 0.6	<0.001

Table I: Baseline characteristics of study participants

The baseline characteristics of the study participants are summarized in Table I. The mean age of patients with type 2 diabetes mellitus (T2DM) was comparable to controls (54.3 ± 9.2 vs. 52.7 ± 8.8 years, p > 0.05). However, body mass index (BMI) was significantly higher in the diabetic group (27.6 ± 3.4 kg/m²) compared to controls (24.2 ± 2.9 kg/m², p < 0.05). Fasting glucose and glycated hemoglobin (HbA1c) levels were markedly elevated in T2DM patients (162.4 ± 38.5 mg/dL and 8.1 ± 1.3%, respectively) compared to controls (89.3 ± 10.2 mg/dL and 5.2 ± 0.6%, respectively; p < 0.001).

Parameter	T2DM Patients (n=120)	Controls (n=120)	p-value
Total cholesterol (mg/dL)	212.6 ± 42.3	178.5 ± 35.4	<0.01
Triglycerides (mg/dL)	198.7 ± 56.8	132.4 ± 41.6	<0.001
HDL-C (mg/dL)	38.2 ± 7.4	48.9 ± 8.2	<0.001
LDL-C (mg/dL)	134.8 ± 36.7	102.3 ± 29.5	<0.01

Table II: Comparison of Lipid profile parameters between T2DM and controls group

Lipid profile analysis (Table II) revealed significantly higher levels of total cholesterol (212.6 ± 42.3 mg/dL vs. 178.5 ± 35.4 mg/dL, p < 0.01), triglycerides (198.7 ± 56.8 mg/dL vs. 132.4 ± 41.6 mg/dL, p < 0.001), and LDL-C (134.8 ± 36.7 mg/dL vs. 102.3 ± 29.5 mg/dL, p < 0.01) in diabetic patients compared to controls. Conversely, HDL-C was significantly reduced in T2DM patients (38.2 ± 7.4 mg/dL vs. 48.9 ± 8.2 mg/dL, p < 0.001).

Parameter	T2DM Patients (n=120)	Controls (n=120)	p-value
Cardiac Risk ratio (CRR)	5.56 ± 1.42	3.64 ± 1.08	<0.001
Atherogenic Coefficient (AC)	4.56 ± 1.42	2.64 ± 1.08	<0.001
Atherogenic Index of Plasma (AIP)	0.42 ± 0.12	0.18 ± 0.09	<0.001
HOMA-IR	4.82 ± 1.56	2.12 ± 0.84	<0.001

Table III: Comparison of Atherogenic indices and insulin resistance between T2DM and controls group

Atherogenic indices (Table III) were consistently elevated in the diabetic group. The mean Cardiac Risk Ratio (CRR) was 5.56 ± 1.42 in T2DM patients compared to 3.64 ± 1.08 in controls (p < 0.001). Similarly, the Atherogenic Coefficient (AC) and Atherogenic Index of Plasma (AIP) were significantly higher in diabetics (AC: 4.56 ± 1.42 vs. 2.64 ± 1.08; AIP: 0.42 ± 0.12 vs. 0.18 ± 0.09; both p < 0.001). Insulin resistance, assessed by HOMA-IR, was markedly elevated in T2DM patients (4.82 ± 1.56 vs. 2.12 ± 0.84, p < 0.001)

Parameter	Pearson Correlation Coefficient (r)	p-value
Triglycerides (TG)	0.482	<0.001
LDL-cholesterol (LDL-C)	0.391	<0.001
Total cholesterol (TC)	0.356	<0.001
HDL-cholesterol (HDL-C)	−0.418	<0.001
Cardiac Risk ratio (CRR)	0.529	<0.001
Atherogenic Coefficient (AC)	0.544	<0.001
Atherogenic Index of Plasma (AIP)	0.612	<0.001

Table IV: Pearson correlation between HOMA-IR and lipid parameters & atherogenic indices in T2DM patients (n= 120)

Correlation analysis (Table IV) demonstrated significant positive associations between HOMA-IR and triglycerides (r = 0.482, p < 0.001), LDL-C (r = 0.391, p < 0.001), and total cholesterol (r = 0.356, p < 0.001). HDL-C showed a significant inverse correlation with HOMA-IR (r = −0.418, p < 0.001). Among the atherogenic indices, HOMA-IR correlated strongly with CRR (r = 0.529, p < 0.001), AC (r = 0.544, p < 0.001), and most notably with AIP (r = 0.612, p < 0.001), suggesting AIP as a robust marker of insulin resistance and cardiovascular risk in T2DM.

DISCUSSION

The present study provides compelling evidence that patients with type 2 diabetes mellitus (T2DM) exhibit profound disturbances in lipid metabolism, elevated atherogenic indices, and increased insulin resistance compared to non-diabetic controls. These findings are consistent with the well-documented phenomenon of diabetic dyslipidemia, which is characterized by hypertriglyceridemia, elevated low-density lipoprotein cholesterol (LDL-C), and reduced high-density lipoprotein cholesterol (HDL-C).[6,7] Such lipid abnormalities are not merely biochemical alterations but represent critical contributors to the pathogenesis of atherosclerosis and cardiovascular disease (CVD), the leading cause of morbidity and mortality among diabetic populations .[4,16,17]

The elevated triglycerides and LDL-C levels observed in our study align with previous reports that insulin resistance promotes hepatic overproduction of very-low-density lipoprotein (VLDL) particles, thereby increasing circulating triglycerides and LDL-C.[2,8] Concurrently, reduced HDL-C levels reflect impaired reverse cholesterol transport, which diminishes the protective role of HDL against atherogenesis.[7] This lipid triad high triglycerides, high LDL-C, and low HDL-C has been recognized as the hallmark of diabetic dyslipidemia and is strongly associated with increased cardiovascular risk.[6] Recent studies have shown that LDL particles in T2DM are often smaller and denser, increasing their atherogenic potential and susceptibility to oxidation.[18,19] Moreover, elevated triglyceride levels are now recognized as an independent cardiovascular risk factor, particularly in patients with metabolic syndrome and diabetes.[18]

Importantly, our study highlights the utility of atherogenic indices Cardiac Risk Ratio (CRR), Atherogenic Coefficient (AC), and Atherogenic Index of Plasma (AIP) as more comprehensive markers of cardiovascular risk than isolated lipid parameters. Recent evidence supports their superiority in predicting cardiovascular events, especially in high-risk populations like T2DM patients.[21,22] Elevated CRR and AC values in T2DM patients indicate a predominance of atherogenic lipoproteins relative to protective HDL-C, thereby reflecting an unfavorable lipid balance.[13] Among these indices, AIP demonstrated the strongest correlation with insulin resistance in our study. This finding is consistent with previous studies showing that AIP is strongly associated with metabolic syndrome, insulin resistance, and cardiovascular risk.[9,20,21] AIP reflects the balance between atherogenic and protective lipoproteins and is closely linked with the presence of small dense LDL particles, making it a sensitive marker of cardiovascular risk.

The mechanistic link between insulin resistance and dyslipidemia was further reinforced by our correlation analysis. Elevated HOMA-IR values were positively associated with triglycerides, LDL-C, CRR, AC, and AIP, while HDL-C showed an inverse relationship. These findings support the hypothesis that insulin resistance drives lipolysis, elevates circulating free fatty acids, and enhances hepatic triglyceride synthesis, ultimately leading to hypertriglyceridemia and reduced HDL-C.[2,8,22] The strong correlation between AIP and HOMA-IR observed in our study suggests that AIP may serve as a surrogate marker of insulin resistance and cardiovascular risk in T2DM patients.

The significant positive correlations observed between HOMA-IR and CRR, AC, and AIP indicate that worsening insulin resistance is associated with a progressively more atherogenic lipid profile. This aligns with growing evidence that insulin resistance plays a key role in vascular inflammation, endothelial dysfunction, and the development of atherosclerosis.[23] The inverse relationship between HDL-C and HOMA-IR further highlights the protective role of HDL, including its anti-inflammatory and antioxidant properties.

Our results are consistent with earlier studies that demonstrated elevated triglycerides, reduced HDL-C, and increased atherogenic indices in diabetic populations.[9,10] These lipid abnormalities have been strongly linked to cardiovascular morbidity and mortality, emphasizing the need for early detection and intervention. Routine evaluation of atherogenic indices, alongside conventional lipid parameters, may enhance risk stratification and guide therapeutic interventions aimed at reducing cardiovascular complications in T2DM.

From a clinical perspective, these findings emphasize the importance of comprehensive cardiovascular risk assessment in T2DM patients. While conventional lipid profiles remain essential, they may underestimate risk in certain individuals. Incorporating atherogenic indices, particularly AIP, into routine clinical evaluation may improve early detection of high-risk patients. Current guidelines recommend a multifactorial approach to cardiovascular risk management, including aggressive lipid control, glycemic management, and lifestyle modification.[16,24]

Furthermore, early identification of insulin resistance and dyslipidemia allows timely intervention through both pharmacological therapies (such as statins and insulin sensitizers) and lifestyle interventions including weight reduction and physical activity. Evidence suggests that such strategies can significantly improve metabolic outcomes and reduce cardiovascular risk.[25]

Despite these strengths, the cross-sectional design of this study limits causal inference. Longitudinal studies are needed to evaluate the predictive role of atherogenic indices in cardiovascular outcomes. Future research incorporating inflammatory markers and advanced lipid parameters may further enhance understanding of the relationship between insulin resistance and atherogenesis.

In conclusion, this study reinforces the critical role of dyslipidemia and insulin resistance in the development of cardiovascular complications in T2DM. Atherogenic indices, particularly AIP, are valuable, cost-effective tools for cardiovascular risk assessment and should be considered in routine clinical practice.

LIMITATIONS

Future research should explore longitudinal associations between these indices and cardiovascular outcomes, as well as the impact of therapeutic interventions targeting insulin resistance and lipid abnormalities. Such studies may provide deeper insights into optimizing cardiovascular risk management in T2DM populations.

CONCLUSION

This study demonstrated that patients with T2DM have significant dyslipidemia, elevated atherogenic indices, and increased insulin resistance compared to healthy individuals. Atherogenic indices showed strong association with insulin resistance and may serve as useful markers for assessing cardiovascular risk. Routine evaluation of lipid profile and atherogenic indices is essential for early detection and prevention of cardiovascular complications in T2DM patients.

FINANCIAL DISCLOSURE

This financial disclosure ensures transparency and confirms that the inclusion of healthy control participants complied with ethical principles, with no direct or indirect financial obligations imposed upon the study participants.

REFERENCES

1. Meena R, Pachori P, Chaudhary S, et al. Level of serum uric 1. American Diabetes Association. Diagnosis and classification of diabetes mellitus. Diabetes Care. 2022;45(Suppl 1): S17–38.
2. DeFronzo RA. Pathogenesis of type 2 diabetes mellitus. Med Clin North Am. 2004;88(4):787–835.
3. International Diabetes Federation. IDF Diabetes Atlas. 10th ed. Brussels: IDF; 2021.
4. World Health Organization. Global report on diabetes. Geneva: WHO; 2016.
5. Gyawali B, Sharma R, Neupane D, Mishra SR, van Teijlingen E, Kallestrup P. Prevalence of type 2 diabetes in Nepal: a systematic review and meta-analysis. Glob Health Action. 2015; 8:29088.
6. Goldberg IJ. Diabetic dyslipidemia: causes and consequences. J Clin Endocrinol Metab. 2001;86(3):965–71.
7. Grundy SM, Benjamin IJ, Burke GL, Chait A, Eckel RH, Howard BV, et al. Diabetes and cardiovascular disease. Circulation. 1999;100(10):1134–46.
8. Reaven GM. Insulin resistance and its consequences. Diabetes. 1988;37(12):1595–607.
9. Dobiasova M. Atherogenic index of plasma as a predictor of cardiovascular risk: theoretical and practical implications. Clin Chem. 2004;50(7):1113–5.
10. Castelli WP, Abbott RD, McNamara PM. Cholesterol and lipoprotein ratios in coronary risk assessment: the Framingham Study. Ann Intern Med. 1983;90(1):85–91.
11. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and beta-cell function in man. Diabetologia. 1985;28(7):412–9.
12. Levin KA. Study design III: Cross-sectional studies. Evid Based Dent. 2006;7(1):24–25.
13. Shrestha N, Karki K, Poudel A, Aryal KK, Mahato NK, Gautam N, et al. Prevalence of diabetes mellitus and associated risk factors in Nepal: findings from a nationwide population-based survey. BMJ Open. 2022;12: e060750. doi:10.1136/bmjopen-2022-060750.
14. Little RR, Rohlfing CL, Sacks DB. The National Glycohemoglobin Standardization Program: Over 20 years of improving HbA1c measurement. Clin Chem. 2014;60(7):1048–1050.
15. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and beta-cell function in man. Diabetologia. 1985;28(7):412–419.
16. American Diabetes Association. Standards of care in diabetes—2024. Diabetes Care. 2024;47(Suppl 1)–S350.
17. International Diabetes Federation. IDF Diabetes Atlas. 11th ed. Brussels: International Diabetes Federation; 2023.
18. Nordestgaard BG. Triglyceride-rich lipoproteins and atherosclerotic cardiovascular disease: new insights from epidemiology, genetics, and biology. Circ Res. 2019;124(4):547–570.
19. Parhofer KG. Interaction between glucose and lipid metabolism: more than diabetic dyslipidemia. Diabetes Metab J. 2020;44(2):188–196.
20. Onat A, Can G, Kaya H, Hergenc G. Atherogenic index of plasma (log10 triglyceride/HDL-cholesterol) predicts high blood pressure, diabetes, and vascular events. Clin Chim Acta. 2019; 492:45–50.
21. Wu TT, Gao Y, Zheng YY, Ma YT, Xie X. Atherogenic index of plasma predicts cardiovascular risk: a meta-analysis. Lipids Health Dis. 2021; 20:26.
22. Samuel VT, Shulman GI. The pathogenesis of insulin resistance: integrating signaling pathways and substrate flux. Cell. 2016;166(3):590–600
23. Ormazabal V, Nair S, Elfeky O, Aguayo C, Salomon C, Zuñiga FA. Association between insulin resistance and the development of cardiovascular disease. Biomed Res Int. 2018; 2018:673–698.
24. Grundy SM, Stone NJ, Bailey AL, Beam C, Birtcher KK, Blumenthal RS, et al. 2018 AHA/ACC guideline on the management of blood cholesterol. Circulation. 2019;139(25)–e1143.
25. Lean MEJ, Leslie WS, Barnes AC, Brosnahan N, Thom G, McCombie L, et al. Primary care-led weight management for remission of type 2 diabetes (DiRECT): an open-label, cluster-randomised trial. Lancet. 2019;393(10170):541–551.