Double Trouble

The term 'double diabetes' was first used by Teupe *et al.*,[1] who noted that a proportion of their type 1 diabetes mellitus (T1DM) patients had a higher insulin requirement, poorer glycaemic control and higher body mass index (BMI) than the rest of their patients. The strong family history of type 2 diabetes mellitus (T2DM) in these patients led the authors to propose the name 'double diabetes'. In the original study by Teupe *et al.*,[1] the prevalence was around 16%. The prevalence of double diabetes appears to have increased rapidly since then. However, the criteria used to define double diabetes may cause variation in the estimated prevalence. Recent data suggest that the BMI of T1DM patients may be higher than in the general population.[2] Using obesity as a criterion, the prevalence of double diabetes would be around 30% while if the presence of metabolic syndrome is used to define double diabetes then the prevalence would be almost 50%.[3] A more accurate way to define double diabetes would be based on insulin sensitivity parameters such as estimated glucose disposal rate (eGDR). A large data set from Sweden suggests that, based on eGDR, the prevalence of double diabetes could be above 50%.[4] A recent study from the United Kingdom reports the prevalence of double diabetes to be even higher (57.9%).[5] The figures from India appear to be more reassuring. A study from Delhi reported double diabetes prevalence to be 7%, while another study from Pune reported metabolic syndrome in 4.5% of patients with T1DM.[6,7] However, the population in Indian studies is younger and possibly from underprivileged sections of society, where obesity may not yet be rampant. Furthermore, these studies did not use eGDR to diagnose double diabetes, which may have led them to report a lower prevalence of double diabetes.

Double diabetes has serious consequences for the complications of diabetes.

Data as far back as that from the Diabetes Control and Complications Trial (DCCT) show that higher baseline insulin resistance (estimated from eGDR) was associated with a higher risk of both macro- and microvascular complications. The prevalence of metabolic syndrome increased from baseline to 9-year follow-up in both conventionally and intensively treated groups.[8] Interestingly, DCCT excluded patients who had obesity, hypertension, hypercholesterolaemia and established vascular disease. In the Pittsburgh Epidemiology of Diabetes Complications (EDC) cohort, the BMI of the patients increased by seven times over a 20-year follow-up period. The 10-year cardiovascular event rate in the Pittsburgh EDC cohort was 10%.[9] The prospective cohort derived from the DCCT, called the Epidemiology of Diabetes Interventions and Complications (EDIC) study, showed that the highest quartile in terms of weight gain in the intensive arm showed the highest increase in cardiovascular risk factors such as blood pressure, low-density lipoprotein (LDL) cholesterol, higher waist: hip ratio and more atherogenic lipid profile.[10]

The risk of microvascular complications with double diabetes is also increased. The SEARCH for diabetes in youth (SEARCH) study reported that obesity, high LDL and low high-density lipoprotein (HDL) were risk factors for peripheral neuropathy in T1DM.[11] Similarly, the risk of cardiac autonomic neuropathy is more in those with obesity and dyslipidaemia.[12] The risk of retinopathy is also higher in obese T1DM.[13]

Under low portal venous insulin concentrations in T1DM (in contrast to T2DM), the activity of hepatic lipase (HL) is reduced—reduced HL activity preserves the HDL cholesterol content of lipoprotein. The emergence of insulin resistance negates this advantage. Most patients with T1DM have high HDL cholesterol; however, a subset of T1DM has lower HDL associated with high triglyceride (TG) and LDL (mimicking T2DM dyslipidaemia). This subset is at a higher risk of cardiovascular events. As reported in the FinnDiane study, poor glucose control combined with obesity and insulin resistance along with an atherogenic lipid profile is among the phenotypes associated with the highest mortality in T1DM. This highlights the importance of recognising and addressing double diabetes.[14]

Factors pointing to the presence of double diabetes include high total daily insulin doses, family history of type 2 diabetes mellitus, central obesity, hypertension and low HDL cholesterol. However, total daily insulin dose does not predict cardiovascular events as well as eGDR does. eGDR has emerged as a sensitive and specific marker of metabolic syndrome in T1DM. An eGDR < 7.32 mg/kg/min had an 85% sensitivity in detecting metabolic syndrome.[15] An Indian study using an eGDR cut-off of 8 mg/kg/min reported that 16.8% of their T1DM subjects had insulin resistance.[16] A recent Indian study found that eGDR estimated by the SEARCH equation had the highest sensitivity and specificity in diagnosing metabolic syndrome in T1DM.[17] Another study from India suggests that parental metabolic syndrome was strongly correlated with metabolic risk and double diabetes.[18]

Strategies to reduce insulin resistance in T1DM can play a crucial role in reducing the mortality associated with double diabetes. Lifestyle intervention can play an important role in this regard. Several small studies have shown that exercise training performed over a 6- to 12-week period can produce improvements in insulin sensitivity ranging from 23 to 60 per cent.[19,20] Improvement in HDL cholesterol along with reductions in LDL cholesterol, waist circumference and blood

pressure has also been noted in T1DM patients after three months of exercise training.[21] Data on the effect of diet on insulin resistance in T1DM are scanty—a recent meta-analysis on the effect of diet on metabolic syndrome in these patients could only include only four eligible studies. Weight loss was present with several dietary strategies, but weight maintenance was seen only with fasting or intermittent fasting regimens. Apart from weight, there were no significant effects on the metabolic syndrome.[22] Although data are lacking, it is understood that an unhealthy diet is a major contributor to weight gain, which is the harbinger of double diabetes.

Studies with thiazolidinediones are not very encouraging. Pioglitazone resulted in weight gain in adolescent T1DM patients, without showing any improvement in insulin dose, haemoglobin A1c (HbA1c) or lipid profile.[23] In a study from India, pioglitazone caused a modest reduction in HbA1c without any changes in insulin requirements, weight or lipid profile.[24] Rosiglitazone also led to weight gain but reduced insulin doses by 11% in overweight adult T1DM subjects.[25] Sodium-glucose transporter-2 (SGLT-2) inhibitors are now approved for adjunctive use with insulin in adult T1DM patients in some countries.[26] While these drugs show the potential for reduction in both insulin doses and weight, the risks of diabetic ketoacidosis and genitourinary infection preclude their widespread use.[27] The cost of these drugs may also be prohibitively high for underprivileged T1DM subjects who are already struggling to bear the cost of insulin and insulin delivery devices.[28] Similarly, limited data with glucagon-like peptide-1 (GLP-1) agonists indicate that they can reduce both insulin doses and body weight in T1DM patients, but the cost of therapy and gastrointestinal adverse effects are important concerns.[29]

With the new brigade of pharmacotherapy having its issues, the spotlight seems to shift to the age-old drug, metformin. Metformin use in T1DM causes a reduction in insulin dose, HbA1c, body weight and cholesterol levels.[30] Similar findings have been reported in more recent studies.[31,32] At the same time, metformin is cheap and rather well tolerated except for mild gastrointestinal complaints. Prevention, it is said, is better than cure. In this issue, Oza *et al*. explore the role of metformin in preventing double diabetes in adolescents with T1DM.[33] They found that a three-month therapy with metformin leads to an almost 50% reduction in the risk of developing double diabetes. Although performed in a small sample, this study is important as very little data are available on double diabetes and its prevention from India. There is an urgent need for more studies with a larger sample size on the prevention of double diabetes. If more data favour the use of metformin, it may be prudent to advise routine use of metformin with insulin in all T1DM patients who are either overweight/obese or have a low eGDR. Considering both the large number of T1DM patients and the rapid increase in obesity rates in India, double diabetes can soon emerge as a major health problem in India. More research work in all aspects of double diabetes in general and its prevention in particular is the need of the hour.

S. V. Madhu, Nishant Raizada

Department of Endocrinology, Center for Diabetes Endocrinology and Metabolism, University College of Medical Sciences and Guru Teg Bahadur Hospital, New Delhi, India

Address for correspondence: Dr. S. V. Madhu, Department of Endocrinology, Center for Diabetes Endocrinology and Metabolism, University College of Medical Sciences and Guru Teg Bahadur Hospital, New Delhi - 110 095, India.
E-mail: drsvmadhu@gmail

References

1. Teupe B, Bergis K. Epidemiological evidence for r e hour.iabetes can soon emerge as 1991;337:361g2.
2. Fellinger P, Fuchs D, Wolf P, Heinze G, Luger A, Krebs M, *et al*. Overweight and obesity in type 1 diabetes equal those of the general population. Wien Klin Wochenschr 2019;131:55qual
3. Kietsiriroje N, Pearson S, Campbell M, Aririion. Wien KlinA. Double diabetes: A distinct high-risk group? Diabetes Obes Metab 2019;21:2609 N,
4. Nystrtr: 2609 N, Pearson S, Campbell M, Aririion. Wien KlinA. Double diabetes: A distinct high-risk group? Diabetes Obes Metabearch work in all aspects. In this iss 2018;20:5569 N.
5. Cantley NW, Lonnen K, Kyrou I, Tahrani AA, Kahal H. The association between overweight/obesity and double diabetes in adults with type 1 diabetes; a cross-sectional study. BMC Endocr Disord 2021;21:187.
6. Mishra BK, Shukla P, Aslam M, Siddiqui AA, Madhu SV. Prevalence of double diabetes in youth onset diabetes patients from east Delhi and neighboring NCR region. Diabetes Metab Syndr 2018;12:839 Shu
7. Oza C, Khadilkar V, Karguppikar M, Ladkat D, Gondhalekar K, Shah N, *et al*. Prevalence of metabolic syndrome and predictors of metabolic risk in Indian children, adolescents and youth with type 1 diabetes mellitus. Endocrine 2022;75:794e of
8. Kilpatrick ES, Rigby AS, Atkin SL. Insulin resistance, the metabolic syndrome, and complication risk in type 1 diabetes: "Double diabetes, Rigby Adiabetes control and complications trial. Diabetes Care 2007;30:707 Car
9. Pambianco G, Costacou T, Ellis D, Becker DJ, Klein R, Orchard TJ. The 30-year natural history of type 1 diabetes complications: The Pittsburgh epidemiology of diabetes complications study experience. Diabetes 2006;55:1463t9.
10. Purnell JQ, Zinman B, Brunzell JD; DCCT/EDIC Research Group. The effect of excess weight gain with intensive diabetes mellitus treatment on cardiovascular disease risk factors and atherosclerosis in type 1 diabetes mellitus: Results from the Diabetes Control and Complications Trial/Epidemiology of diabetes interventions and complications study (DCCT/EDIC) study. Circulation 2013;127:180t7.
11. Jaiswal M, Divers J, Dabelea D, Isom S, Bell RA, Martin CL, *et al*. Prevalence of and risk factors for diabetic peripheral neuropathy in youth with type 1 and type 2 diabetes: SEARCH for diabetes in youth study. Diabetes Care 2017;40:1226reth
12. Franceschi R, Mozzillo E, Di Candia F, Rosanio FM, Leonardi L, Liguori A, *et al*. A systematic review of the prevalence, risk factors and screening tools for autonomic and diabetic peripheral neuropathy in children, adolescents and young adults with type 1 diabetes. Acta Diabetol 2022;59:293tic r
13. Price SA, Gorelik A, Fourlanos S, Colman PG, Wentworth JM. Obesity is associated with retinopathy and macrovascular disease in type 1 diabetes. Obes Res Clin Pract 2014;8:e178-82.
14. M.kinen V-P, Forsblom C, Thorn LM, Wadolman PG, Wentworth JM. Obes, *et al*. Metabolic phenotypes, vascular complications, and premature deaths in a population of 4,197 patients with type 1 diabetes. Diabetes 2008;57:2480v7.
15. Ferreira-Hermosillo A, Ibarra-Salce R, Rodrodrre deaths in a population of 4,197 patients with type 1 diabetescular disease in type 1 diabetes. Obes with double diabetes. BMC Endocr Disord 2020;20:87.
16. Pathak V, Mishra I, Baliarsinha AK, Choudhury AK. Prevalence of insulin resistance in type 1 diabetes mellitus and its correlation

with metabolic parameters: The double trouble. Eurasian J Med 2022;54:107 J M
17. Oza C, Khadilkar A, Karguppikar M, Gondhalekar K, Khadilkar V. Comparison of insulin sensitivity indices for detection of double diabetes in Indian adolescents with type 1 diabetes. J Pediatr Endocrinol Metab JPEM 2022;35:1010l9.
18. Oza C, Karguppikar M, Khadilkar V, Gondhalekar K, Khadilkar A. A pilot study to determine association of parental metabolic syndrome with development of metabolic risk in Indian children, adolescents and youth with Type-1 diabetes. Diabetes Metab Syndr 2022;16:102453.
19. Yki-Ji-J02453.ikar M, Khadilkar V, Gondhaleormalization of insulin sensitivity in type I diabetic subjects by physical training during insulin pump therapy. Diabetes Care 1984;7:52047.
20. Landt KW, Campaigne BN, James FW, Sperling MA. Effects of exercise training on insulin sensitivity in adolescents with type I diabetes. Diabetes Care 1985;8:461C5.
21. Lehmann R, Kaplan V, Bingisser R, Bloch KE, Spinas GA. Impact of physical activity on cardiovascular risk factors in IDDM. Diabetes Care 1997;20:1603Kapl
22. Thackrey E, Chen J, Martino C-R, Preda V. The effects of diet on weight and metabolic outcomes in patients with double diabetes: A systematic review. Nutrition 2022;94:111536.
23. Zdravkovic V, Hamilton JK, Daneman D, Cummings EA. Pioglitazone as adjunctive therapy in adolescents with type 1 diabetes. J Pediatr 2006;149:845V9.
24. Bhat R, Bhansali A, Bhadada S, Sialy R. Effect of pioglitazone therapy in lean type 1 diabetes mellitus. Diabetes Res Clin Pract 2007;78:349nsal
25. Strowig SM, Raskin P. The effect of rosiglitazone on overweight subjects with type 1 diabetes. Diabetes Care 2005;28:1562 7.
26. Vitale RJ, Laffel LM. Sodium-glucose transporter inhibition in adult and pediatric patients with type 1 diabetes mellitus. Adv Chronic Kidney Dis 2021;28:309roni
27. Garg SK, Henry RR, Banks P, Buse JB, Davies MJ, Fulcher GR, *et al*. Effects of sotagliflozin added to insulin in patients with type 1 diabetes. N Engl J Med 2017;377:2337adde
28. El Masri D, Ghosh S, Jaber LA. Safety and efficacy of sodium-glucose cotransporter 2 (SGLT2) inhibitors in type 1 diabetes: A systematic review and meta-analysis. Diabetes Res Clin Pract 2018;137:83, Gh
29. Liu L, Shao Z, Xia Y, Qin J, Xiao Y, Zhou Z, *et al*. Incretin-based therapies for patients with type 1 diabetes: A meta-analysis. Endocr Connect 2019;8:277sis.
30. Vella S, Buetow L, Royle P, Livingstone S, Colhoun HM, Petrie JR. The use of metformin in type 1 diabetes: A systematic review of efficacy. Diabetologia 2010;53:809 rev
31. Libman IM, Miller KM, DiMeglio LA, Bethin KE, Katz ML, Shah A, *et al*. Effect of metformin added to insulin on glycemic control among overweight/obese adolescents with type 1 diabetes: A randomized clinical trial. JAMA 2015;314:2241nica
32. Bjornstad P, SchSchtrialn on glycemic control among overweight/obese ad. Metformin improves insulin sensitivity and vascular health in youth with type 1 diabetes mellitus. Circulation 2018;138:2895t907.
33. Oza C, Mondkar S, Shah N, More C, Khadilkar V, Khadilkar A. A pilot study to assess effect of metformin therapy on prevention of double diabetes in Indian adolescents with type-1 diabetes. Indian J Endocr Metab 2023;27:210-6.

Access this article online

Quick Response Code:

Website: https://journals.lww.com/indjem/

DOI: 10.4103/2230-8210.379597

How to cite this article: Madhu SV, Raizada N. Double trouble. Indian J Endocr Metab 2023;27:189-91.