International Journal of Research in Medical Sciences
Kansara S et al. Int J Res Med Sci. 2022 Nov;10(11):2597-2601
www.msjonline.org
pISSN 2320-6071 | eISSN 2320-6012
DOI: https://dx.doi.org/10.18203/2320-6012.ijrms20222865

Original Research Article

A study of prevalence of autoantibodies in lean or underweight diabetic subjects in Southern Rajasthan

Sandeep Kansara[1]*, Akhlaq Hasan[2], Shuchi Goyal[2]

[1]Department of Endocrinology, [2]Department of Biochemistry, Rabindranath Tagore Medical College, Udaipur, Rajasthan, India

Received: 18 September 2022
Revised: 11 October 2022
Accepted: 14 October 2022

***Correspondence:**
Dr. Sandeep Kansara,
E-mail: drsandeepkansara@yahoo.co.in

ABSTRACT

Background: The prevalence of diabetes mellitus (DM) is increasing day by day. Changing life style and unhealthy eating habits are major contributor to this pandemic, however certain individuals develop diabetes despite enough physical activity and low to normal body weight, even in absence of family history. The current study aimed to assess the autoantibody profile of these underweight/lean diabetic subjects, in order to better understand their aetiology.
Methods: This cross sectional, observational study was carried out in endocrinology OPD and ward of RNT Medical College, Udaipur, Rajasthan (India). The study included consecutive 207 lean/underweight diabetic subjects, on insulin or oral antidiabetic drugs (OAD), with or without history of ketosis and negative family history of diabetes. After detailed history and anthropometric examination, subjects were screened for presence of autoantibodies to GAD, TPO and IgA tTG.
Results: 9 subjects were excluded from analysis (7 pancreatic calcification, 2 incomplete data). Out of 198 subjects, 153 (77.3%) subjects tested positive for GAD antibodies, while Anti TPO and IgA anti tTG antibodies were positive in 50 (25.3%) and 6 (3.0%) subjects, respectively. 39 (19.69%) subjects tested positive for both anti GAD and anti TPO antibodies and only 1(0.505%) subject had all the 3 antibodies present. Of the total study population, 158 (79.8%) subjects were on insulin, while 13 (6.6%) subjects received OAD, and 27 (13.6%) subjects both insulin and OAD.
Conclusions: Lean/underweight diabetic subjects with negative family history of diabetes should be screened for presence of autoimmune markers for type 1 diabetes mellitus, irrespective of their treatment.

Keywords: GAD, Lean diabetes, TPO

INTRODUCTION

Diabetes mellitus (DM) is a common metabolic disorder associated with significant morbidity and mortality. India has large diabetic population, next to China only. The prevalence of diabetes is increasing day by day; not only of type 2 DM, but also of type 1 DM. Progressively increasing sedentary life style and unhealthy eating habits due to rapid urbanization can explain majority of type 2 diabetes, however there are certain individuals who despite having enough physical activity and normal to low body weight develop diabetes, even in absence of positive family history of diabetes. These subjects often respond to oral antidiabetic drugs initially but frequently require insulin from early stage of their disease for glycemic control and survival, even in absence of ketosis. These subjects have been previously described by WHO as MRDM (malnutrition related diabetes mellitus) having clinical characteristics as, early onset of diabetes- usually under 30 years of age, insulin-requiring (to obtain adequate glycemic control), not ketosis-prone, absence of imaging evidence of pancreatic calculi or ductal dilatation

and low body mass index BMI (usually below 17 kg/m^2) with other clinical features of malnutrition and often with growth retardation.[1] In some developing countries, non-obese patients constitute the more common category, and a proportion of them have BMI of less than 18.5 kg/m^2. Many factors are not well understood in these subjects with NIDDM and low body weight. Further research is thus required in this group.[2]

In India, however, low bodyweight type 2 diabetics constitute 11 to 25% of the diabetic population.[3] Their leanness has been attributed to their inherent characteristics and to their diabetic state, malnutrition or low socio-economic status.

Different studies have shown that these subjects had persistently severe hyperglycemia with low circulating insulin levels. They were therefore confused with late-onset type 1 DM or latent autoimmune diabetes in adults (LADA).[4]

In southern Rajasthan, we often encounter such situation where it is difficult to categorize these subjects to type 1 or type 2 DM on the basis of history and clinical examination alone. Though no systemic data is available, the common experience is that these subjects do not fit in type 2 DM but they are atypical for type 1 DM also. The situation is further complexed by the fact that many tribes reside in this part of Rajasthan, having different eating habits, and majority of them are malnourished. Thus, altogether it becomes important to see the contribution of their nutrition, life style and environment on causing pancreatic dysfunction, as well as autoimmunity. Evaluation for antibodies against insulin or pancreatic beta cells, thyroid and other gut antigens may be helpful in correctly classifying these individuals.

The purpose of this study was to evaluate the autoantibody profile of these lean/underweight, physically active diabetic subjects, to know the exact etiology of their diabetes.

METHODS

This observational study was carried out in the endocrinology OPD and ward of RNT Medical College, Udaipur (a tertiary care centre in Southern Rajasthan) between march 2020 and March 2021, after approval by local research ethics committee and obtaining due consent from subjects. The study population included 198 lean/underweight diabetic subjects (both existing and newly diagnosed), on insulin or oral antidiabetic drugs with or without history of ketosis and Absence of positive family history of diabetes.

Inclusion criteria

Lean (BMI 18.5-22.9 kg/m^2) and or underweight (BMI <18.5 kg/m^2) diabetic subjects on insulin or oral antidiabetic drugs. Absence of positive family history of diabetes and with or without history of ketosis.

Exclusion criteria

Obese or overweight diabetic individuals, gestational diabetes mellitus, secondary diabetes mellitus-pancreatitis, post pancreatectomy, steroid induce DM, lipodystrophy, congenital insulin resistance syndrome.

230 consecutive study subjects were evaluated for enrolment in the study. After briefing about the study and its purpose, 207 subjects consented for participation. During evaluation 7 subjects were excluded due to presence of pancreatic calcification and 2 subjects not included for analysis due to missing data.

Investigations

Subjects were recruited from endocrinology OPD and ward during their routine visits or hospitalization. 15 ml of blood sample was collected for the following investigations, irrespective of their meal status. Complete blood counts (CBC), random blood glucose (RBG), glycosylated hemoglobin (HbA1c), renal function tests (RFT), liver function tests (LFT), lipids, anti-GAD (glutamic acid decarboxylase) antibodies, anti TPO (thyroid peroxidase) antibodies, anti IGA tTG (tissue transglutaminase) antibodies. USG abdomen was done to rule out pancreatic calcification. Biochemical analysis was done in Siemens Autoanalyzer using Flex® reagent cartridges. Anti-GAD, TPO and IgA Anti tTG antibodies were measured by ELISA using kits supplied by Biomerica, Calbiotic and Orgentec, respectively.

Statistical analysis

Categorical and continuous variables are expressed as mean±SD, as percentage, as range. Parameters were analysed using χ^2 test for categorical data and the "t" test for continuous data. Statistical analysis was done using JASP 0.16.1 version. A "p" value of <0.05 was considered as significant.

RESULTS

Out of 207 subjects, 9 subjects were excluded for various reasons (7 for pancreatic calcification, 2 for missing data) and remaining 198 subjects were observed for presence of autoantibodies. Out of 198 subjects, 153 (77.3%) subjects tested positive for GAD antibodies, 50 (25.3%) subjects positive for anti TPO antibodies, and 39 (19.69%) subjects tested positive for both GAD and anti TPO antibodies. 6 (3.0%) subjects were sero positive for IgA anti tTG antibodies. 1 (0.505%) subject had all the 3 auto antibodies positive. Mean age of study subjects was 35.5±13 years (age range 12-74 years). Of the total study population 85 (42.9%) were females and 113 (57.1%) were males.

Table 1: Demographic and clinical profile of study subjects.

Parameter	Mean±SD
Total subjects	198
Males	113 (57.1%)
Females	85 (42.9%)
Mean age (years)	35.5±13 (12-74)
Males	36.4±13.1 (14-74).
Females	34.2±12.7 (12-68)
Weight (kg)	49.3±8.0 (22-68)
Males	51.7±8.0 (22-68)
Females	46.1±6.7 (26-61)
BMI (kg/m^2)	19.2±2.5
Males	19.2±2.61
Females	19.3±2.3
Height (cm)	159.7±9.1
Males	163.8±8.6
Females	154.2±6.3
Duration of diabetes (years)	7.4±6.5 (0-27)
Males	8.1±6.6 (0-25)
Females	6.4±6.4 (0-27)
Waist circumference (cm)	74.8±6.9
Hip circumference (cm)	83.9±6.9
WHR	0.89±0.03
Autoantibody status	
GAD +ve	153 (77%)
TPO +ve	50 (25.3%)
IgA tTG +ve	6 (3.0%)
GAD and TPO +ve	39 (19.6%)
GAD, TPO and IgA tTG +ve	1 (0.505%)
HbA1c (%)	10.3±2.8 (5.4-21.4)
GAD+ve	10.2±2.6 (5.4-17.5)
GAD –ve	10.8±3.6 (6.5-21.4)
Presenting symptoms at the time of diagnosis	
Ketosis	57 (28.7%)
Osmotic symptoms (polyuria, polydipsia, polyphagia)	162 (81.8%)
Weakness	89 (44.9%)
Weight loss	80 (40.4%)
Current treatment	
Insulin only	158 (79.8%)
Insulin and OAD	27 (13.6%)
OAD only	13 (6.6%)

Mean weight and BMI of study subjects were 49.34±8.01 kg (22-68 kg) and 19.2±2.5 kg/m^2, respectively. Mean duration of diabetes was 7.4±6.5 years (range 0.0-27.0 years). Most common presenting symptoms at the time of diagnosis were polyuria, polydipsia and polyphagia in162 (81.8%) subjects, while ketosis was reported in 57 (28.7%) of subjects only. History of weight loss was present in 80 (40.4%) subjects while weakness was reported by 89 (44.9%) subjects. Of the total study population, 158 (79.8%) subjects were on insulin only while 13 (6.6%) subjects were taking oral antidiabetic drugs and remaining 27 (13.6%) subjects were taking both insulin and OAD. Mean age of GAD positive subjects was 35.5±12.2 years (range 12.0-70.0 years). Out of 153 GAD positive subjects 62 (40.5%) subjects were females and 91 (59.5%) were males.

Mean age at diagnosis of subjects with ketosis was 29.8±12.8 years (12-65 years) versus 37.9±13.4 years (12-70 years), p value <0.01, for those with no ketosis. GAD antibodies were positive in 31 (77.5%) individuals with ketosis while 69 (70.4%) individuals with no ketosis, p value 0.48. Ketosis was more common in those with GAD antibodies positive 31 (31%) subjects versus 7 (21.2%), p value 0.48, in those with GAD antibodies negative. As far as treatment is concerned, 37 (92.5%) subjects with history of ketosis were on insulin versus 79 (80.6%) subjects, p value 0.218, with no history of ketosis.

The demographic and clinical data are summarized in Table 1.

DISCUSSION

Lean diabetes has been commonly reported from South Asia as well as from African countries, Uganda and Ethiopia.[5-9] The prevalence of lean diabetes is quite variable among different populations ranging from 5.4% in India to 32 % in Africa.[10,11]

Not only South Asians have higher prevalence of type 2 DM but it occurs at younger age and lower level of BMI compared with Caucasians.[12]

Pathogenesis of lean diabetes may be quite heterogenous, but broadly divided into autoimmune and nonautoimmune category. KMV Narayan et al have shown that SA with normal BMI had 5 times the diabetes prevalence in comparison to normal whites and impaired insulin secretion may be more important than insulin resistance.[13]

In southern Rajasthan, many tribes reside, having farming as their predominant occupation. These individuals are often malnourished, having lean built. The general observation is that these subjects do not have typical clinical features of both type 2 DM (like obesity, positive family history of diabetes, sedentary life style), as well as type 1 DM (history of ketosis, inability to survive without insulin). Such individuals have been previously also described by Ahuja et al, who categorized a broad subset of subjects mostly of Asian and African ethnicity under the following criteria: (1) blood glucose >200; (2) onset <30 years of age; (3) BMI <18 kg/m^2; (4) absence of ketosis on insulin withdrawal; (5) poor socio-economic status or history of childhood malnutrition.[14]

In order to correctly classify these subjects, the current study aimed at detecting antibodies against GAD, tTG and TPO antigens. Out of 198 subjects studied, 153 (77.3%) subjects exhibited positivity to GAD antibodies.

Our study corroborated with the findings, as well added evidence to findings of Singh et al, who in 2000 observed that immunological studies on subjects with malnutrition-modulated diabetes mellitus in India have shown that many are positive for GAD antibodies.[15]

Our study has shown relative preponderance of males, where 113 (56.5%) subjects were male out of total 198. Fekadu et al had also described phenotypic similarities, demonstrating a male preponderance with the most extensive data being described from Ethiopia.[16]

Singh et al studied various autoantibodies in 34 Type 1 DM subjects and found 14.7% were positive for IgA anti tTG.[17]

Pulikkal et al studied 258 subjects with type 1 diabetes and reported that 12 (4.65%) were found to be positive for IgA Anti tTG antibodies. Distribution of IgA Anti tTG positivity was equal in both sexes. Our study group demonstrated 6 (3.0%) subjects having IgA Anti tTG antibodies positive. These results are in close agreement with findings of Pulikkal et al.[18]

Anti TPO antibodies were positive in 50 (25.3%) subjects of our study. Thus, present study confirms that type 1 diabetes is frequently associated with other organ specific autoantibodies.

The GAD negative subjects of our study might be having either lean type 2 DM or type 1 DM with gradual decline of antibodies titer. Type 2 diabetes mellitus in lean undernourished individuals can be explained by hypothetical DOHaD (developmental origins of health and disease) concept. According to which, undernutrition during critical windows of development may impair organ development, leading to small beta cell mass, or may impair beta cell replication or neogenesis or induce metabolic/ epigenetic changes that ultimately lead to increased risk of metabolic diseases such as type 2 diabetes later in life.[19,20]

Strengths of this study are that this is the first study generating data from this part of country. The current study included large number of lean/underweight subjects with diabetes, who were lacking typical clinical features of both type 1 and type 2 DM. We tested for multiple antibodies (autoimmunity beyond islets) which are commonly associated with type 1 DM. We used rigorous protocol to clinically exclude possible type 2 DM individuals as well as those having secondary/FCPD (fibro calculous pancreatic diabetes) or genetic insulin resistance syndrome.

Limitations of this study are that we included diabetic subjects irrespective of their duration of diabetes. Ours is a tertiary care hospital, hence there may be selection bias. Our study subjects had wide age range. We did not measure serum C-peptide and insulin levels in these subjects. Family history may be negative in subjects with type 2 DM and hence it does not rule out type 2 DM.

CONCLUSION

Majority of our study subjects (77.3%) had autoantibodies for GAD antigen and (25.3%) and (3%) subjects were tested positive for both TPO and TTG antibodies, respectively, thus confirming the fact that type 1 DM often coexist with other autoimmune disorders. The results suggest that autoimmunity is a common cause of diabetes mellitus in lean/underweight, physically active diabetic subjects with negative family history in southern Rajasthan, especially those requiring insulin since the time of diagnosis of diabetes or early in the course of treatment.

From the results of current study, it was concluded that screening for antibodies in lean/underweight diabetics should be encouraged even in absence of classical features of type 1 diabetes mellitus for appropriate diagnosis and better management of these individuals.

ACKNOWLEDGEMENTS

The financial support provided by multi-disciplinary research unit (department of health research), RNT Medical college, Udaipur to carry out this study is greatly acknowledged. The help rendered by Indrajeet Yadav, Sachin Kumar Solanki and Lalit Kishor for collecting samples and Shelesh Kumar Swami and Nitesh Kumar Chauhan for processing samples is gratefully acknowledged.

Funding: Financial support provided by multi-disciplinary research unit (Department of Health Research), RNT, Medical college, Udaipur
Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee RNT Medical College, Udaipur, Rajasthan, India

REFERENCES

1. Diabetes mellitus. Report of a WHO Study Group. World Health Organ Tech Rep Ser. 1985;727:1-113.
2. Hoet JJ, Tripathy BB. Consensus statement from the international workshop on types of diabetes peculiar to the tropics, 17-19 October 1995, in Cuttack, India. Acta Diabetol. 1996;33:62-4
3. Mohan V, Alberti KGMM. Diabetes in the tropics. In: DeFronzo RA, Ferrannini E, Zimmet P, Alberti G, eds. International textbook of diabetes mellitus. John Wiley and Sons; 1991:177-196
4. Zimmet PZ, Tuomi T, Mackay IR, autoimmune diabetes mellitus in adults (LADA): The role of anti-bodies to glutamic acid decarboxylase in diagnosis and prediction of insulin dependency. Diabetes Med. 1994;11:299-303.

5. Mohan V, Vijayaprabha R, Rema M, Premalatha G, Poongothai S, Deepa R, et al. Clinical profile of lean NIDDM in South India. Diabetes Res Clin Pract. 1997;38(2):101-8. Erratum in: Diabetes Res Clin Pract. 1998;41(2)149-50.
6. Unnikrishnan R, Anjana RM, Mohan V. Diabetes in south Asians: is the phenotype different? Diabetes. 2014;63(1):53-5.
7. Mayega RW, Guwatudde D, Makumbi F, Nakwagala FN, Peterson S, Tomson G, et al. Diabetes and pre-diabetes among persons aged 35 to 60 years in eastern Uganda: prevalence and associated factors. PloS One. 2013;8(8):e72554.
8. Bahendeka S, Wesonga R, Mutungi G, Muwonge J, Neema S, Guwatudde D (2016) Prevalence and correlates of diabetes mellitus in Uganda: a population-based national survey. Trop Med Int Health. 2016;21(3):405-16.
9. Animaw W, Seyoum Y (2017) Increasing prevalence of diabetes mellitus in a developing country and its related factors. PLoS One. 2017;12(11):e0187670.
10. Gujral UP, Mohan V, Pradeepa R, Deepa M, Anjana RM, Narayan KM. Ethnic differences in the prevalence of diabetes in underweight and normal weight individuals: the CARRS and NHANES studies. Diabetes Res Clin Pract. 2018;146:34-40.
11. Kibirige D, Sekitoleko I, Lumu W, Jones AG, Hattersley AT, Smeeth L, et al. Understanding the pathogenesis of lean non-autoimmune diabetes in an African population with newly diagnosed diabetes. Diabetologia. 2022;65(4):675-83.
12. Anjana RM, Deepa M, Pradeepa R, Mahanta J, Narain K, Das HK, et al. Prevalence of diabetes and prediabetes in 15 states of India: results from the ICMR–INDIAB population-based cross-sectional study. Lancet Diabetes Endocrinol. 2017;5(8):585-96.
13. Narayan KV, Kondal D, Daya N, Gujral UP, Mohan D, Patel SA, et al. Incidence and pathophysiology of diabetes in South Asian adults living in India and Pakistan compared with US blacks and whites. BMJ Open Diabetes Res Care. 2021;9(1):e001927.
14. Ahuja MM. Diabetes-special problems in developing countries. Bull Deliv Health Care Diabetics Develop Countries 1980;1:5-6.
15. Singh AK, Bhatia E, Dabadghao P, Bhatia V, Gellert SA, Colman PG. Role of islet autoimmunity in the aetiology of different clinical subtypes of diabetes mellitus in young north Indians. Diabetes Med. 2000;17(4):275-80.
16. Fekadu S, Yigzaw M, Alemu S, Dessie A, Fieldhouse H, Girma T, et al. Insulin-requiring diabetes in Ethiopia: associations with poverty, early undernutrition and anthropometric disproportion. Eur J Clin Nutr. 2010;64:1192-8.
17. Singh S, Singh G, Agrawal NK, Singh RG, Kumar SB. Prevalence of autoantibodies and HLA DR, DQ in type 1 diabetes mellitus. J Clin Diagn Res. 2016;10(7):EC09.
18. Pulikkal AA, Kolly A, Prasanna Kumar KM, Shivaprasad C. The seroprevalence of immunoglobulin A transglutaminase in type 1 diabetic subjects of South Indian origin. Indian J Endocrinol Metab. 2016;20(2):233-7.
19. Hoffman DJ, Reynolds RM, Hardy DB. (2017) Developmental origins of health and disease: current knowledge and potential mechanisms. Nutr Rev. 2017;75(12):951-70.
20. Mandy M, Nyirenda M. Developmental origins of health and disease: the relevance to developing nations. Int Health. 2018;10(2):66-70.

Cite this article as: Kansara S, Hasan A, Goyal S. A study of prevalence of autoantibodies in lean or underweight diabetic subjects in Southern Rajasthan. Int J Res Med Sci 2022;10:2597-601.