Original Article

Resting Metabolic Rate in Indian Adolescents and Youth with Type 1 Diabetes Mellitus: A Case Controlled Study

Madhura Karguppikar[1], Shruti Mondkar[1], Nikhil Shah[1], Neha Kajale[1,2], Sarita Kulkarni[3], Ketan Gondhalekar[1], Shital Bhor[1], Vaman Khadilkar[1,2], Anuradha Khadilkar[1,2]

[1]Hirabai Cowasji Jehangir Medical Research Institute, Jehangir Hospital, [2]Interdisciplinary School of Health Sciences, Savitribai Phule University, [3]Endocrine and Growth Unit, Jehangir Hospital, Pune, Maharashtra, India

Abstract

Introduction: Energy metabolism in type 1 diabetes (T1D) is known to be different. Resting metabolic rate (RMR) accounts for the largest portion of total energy needs. The objective of our study was to assess resting metabolic rate and its determinants in adolescents and young adults with T1D in comparison with age- and gender-matched healthy controls. **Methods:** This cross-sectional study included 97 children and young adults (10–19 years) with type 1 diabetes having a disease duration of at least 1 year. For the control population, 95 age- and gender-matched healthy adolescents were enrolled. Clinical examination and biochemical evaluation of parameters pertaining to diabetes and body composition were estimated, and RMR was measured using indirect calorimetry for both cases and controls. **Results:** Adolescents with T1D were significantly shorter, and had significantly lower calorie intake, higher RMR and volume of oxygen consumed (VO_2) as compared to the healthy controls ($P < 0.05$). RMR adjusted for weight showed a significant positive correlation with lean body mass (LBM) percentage, and energy intake and a negative correlation with disease duration. Those with a T1D duration of less than 5 years demonstrated a significantly higher RMR, lower body fat percentage, higher LBM percentage, carbohydrate and energy intake/kg body weight and higher calculated insulin sensitivity (IS) as compared to those with greater disease duration. Muscle mass percentage and higher energy intake were found to be significant positive predictors and advancing age/diabetes duration was a negative predictor of weight-adjusted RMR ($P < 0.05$), whereas IS and male gender tended towards significant negative association ($P = 0.06$). **Conclusion:** Indian children with type 1 diabetes had a higher resting metabolic rate as compared to healthy children. Muscle mass, energy intake and diabetes duration were observed to be important predictors of RMR in T1D. Reduction in RMR with advancing age/disease duration may predispose to weight gain and subsequent double diabetes in T1D.

Keywords: Children and young adults, India, resting metabolic rate, type 1 diabetes

Introduction

Type 1 diabetes (T1D) is an autoimmune disorder that causes insulin deficiency.[1] T1D commonly presents in childhood or adolescence and the International Diabetes Federation (IDF) Atlas 2021 estimates that over 1.2 million children and adolescents suffer from T1D globally; of these, nearly 50% are below 15 years of age. India is estimated to have the highest incidence and prevalence of T1D in children and adolescents as of 2021.[2]

Energy metabolism in T1D is known to be different due to the insulin-deficient state; resting metabolic rate (RMR), also called resting energy expenditure, accounts for the largest portion of total energy needs.[3] RMR is defined as the amount of energy expended when an individual is awake and in a postabsorptive state, whereas having not exercised for 12 h.[4] Resting and basal metabolic rate (BMR) are often used interchangeably; however, they differ in that BMR is usually measured under very restrictive conditions (under a thermally neutral environment, needs a specialised testing facility, etc.) and is harder to assess than RMR.[5] Reports suggest that RMR

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Address for correspondence: Dr. Anuradha Khadilkar, Hirabai Cowasji Jehangir Medical Research Institute, Jehangir Hospital, Pune, Maharashtra, India.
E-mail: anuradhavkhadilkar@gmail.com

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may be a better indicator of daily energy needs than BMR.[6] RMR is known to be influenced by body composition, gender and age. Increases in muscle mass, reduction in body fat and male gender (due to more muscle mass as compared to females) are known to positively impact RMR.

There is increasing evidence of the occurrence of insulin resistance (IR) in patients with T1D, the pathogenesis of which is multifactorial; obesity is a major determinant of IR in T1D. Although the HOMA IR gives an estimate of IR, it cannot be utilised in T1D due to negligible endogenous insulin production, and the influence of exogenously administered insulin. Further, although the hyperinsulinaemic-euglycaemic clamp studies are the gold standard for the diagnosis of IR in T1D, they are cumbersome. As a result, various equations have been developed to estimate calculated insulin sensitivity (IS), which are in consonance with clamp study results.[7] A study by the author's group on the comparison of methods for the calculation of IS in T1D observed that the SEARCH equation was the most sensitive.[8]

RMR and IR have a complex cause–effect relationship; studies have demonstrated reduced RMR to be associated with weight gain and IR.[9] Conversely, IR has been demonstrated to be a negative predictor of RMR.[10] The majority of the studies on RMR have been conducted in adults and a few studies have evaluated the effect of obesity, age, puberty and gender on RMR in children/adolescents.[11-13] To the best of our knowledge, there are no such studies in children/adolescents with T1D. Recently, fat oxidation rate during exercise was explored in 12 pre-pubertal children with T1D. RMR and fat oxidation rates were found to be higher in children with T1D. Because T1D is known to be an insulin-deficient catabolic state, it would be interesting to study its impact on RMR.[14] Also, RMR is known to be a risk factor for future weight gain, and little is known about the factors determining its level in T1D. The assessment of RMR in T1D may also provide insights into the role of RMR in the development of weight gain and IR in T1D.

Thus, the objective of our study was to assess RMR and its determinants in adolescents and young adults with T1D in comparison with age- and gender-matched healthy controls.

Materials and Methods

Subjects

The study was conducted at a multidisciplinary clinic ("Sweetlings" project-provides insulin, glucometers, and strips for testing, consultations for children/youth with T1D from middle/lower socioeconomic classes) of tertiary level care hospital at Pune (Western India) from September 2019 to April 2020. All adolescents with T1D between 10 and 19 years with at least 1-year disease duration were approached to take part in this cross-sectional, case–control study. Younger children were unable to undergo the RMR test because it required them to remain inactive for a protracted period. Of 252 adolescents and young adults in this age group, 103 subjects (and their parents) were approached and they agreed to take part in the study. Children under 10 years, those with celiac disease, untreated hypothyroidism/hyperthyroidism, polyendocrinopathies or those on other medications were excluded (n = 6). None of the participants were involved in any competitive sports. For the control population, 95 age- and gender-matched healthy adolescents were enrolled from nearby schools and junior colleges. Approval was obtained from the institutional ethics committee (The Institutional Biomedical and Health Research Ethics Committee, Jehangir Clinical Development Center Pvt. Ltd.) before the study on August 7, 2019. A written, informed consent was obtained from parents, and participants gave assent. All procedures followed the guidelines laid down in the Declaration of Helsinki (2013).

Clinical history and examination

History (age, diabetes duration, current medications, insulin regimen, total dose of insulin per day and dietary intake [24-h dietary recall]) was noted. Similar details (except details on diabetes) were recorded for the control group. Sexual maturity staging of children with diabetes (Tanner staging) was performed by a paediatric endocrinologist.

Anthropometry

In both groups, weight was measured using an electronic scale, and standing height was measured using a portable stadiometer (Leicester Height Meter, Child Growth Foundation, UK). Body mass index (BMI) was calculated and height, weight and BMI were converted to Z-scores.[15]

Biochemical measurements

A fasting blood sample (5 mL) was drawn from T1D participants. Glycaemic control was evaluated by measuring glycosylated haemoglobin (HbA1C, high-performance liquid, BIO-RAD, Germany). Thyroid status was evaluated by measurement of thyroid-stimulating hormone (TSH) concentrations and free T4 using the Chemiluminescent Microparticle Immuno Assay.

Body composition (BC)

After a minimum of 3 h of fasting and voiding before measurement, BC was measured using a body impedance analyser (BIA-Model BC-420MA, Tanita, Tokyo, Japan) as per the manufacturer's instructions in both groups. BIA measures BC as fat percentage, fat and fat-free mass (FMM) and total body water. Using the total body weight obtained from the analyser, the lean mass percentage was calculated and Z-scores were computed for body fat percentage and lean mass percentage.[16]

Calculated insulin sensitivity (IS)

IS was calculated using the SEARCH equation[7]:

Exp[4.64725–0.02032 (waist; cm)–0.09779 (HbA1c; %)–0.00235 (triglyceride; mg/dL)]

As a cut-off of 5.485 mg/kg/min was found to have the highest sensitivity and specificity in a previous study by the author's group, this was considered as the criterion for the conversion of the IS variable into categorical data for linear regression.[8]

Resting metabolic rate measurements

Fitmate GS(TM) equipment (COSMED SRL, Italy) was used to measure RMR during the early morning period (before insulin administration). After measuring anthropometry, the subject was made to rest for 10 min before starting measurements. The test procedure was explained in the language he/she could understand, and the subject was made to wear an appropriate-sized face mask (sterilised after each measurement). Room noise, temperature and lighting were controlled, and the subject remained seated and was asked to relax and remain awake throughout the measurement (25 min). After achieving a steady state, the test was considered complete. The procedure was carried out by a trained technician, under the observation of a paediatrician. RMR was estimated using the modified Weir equation in Kcal/day from the equipment (RMR [kcal/day] = 1.44 × (3.9 × VO_2 [ml/min] +RQ × VO_2 [mL/min]), where, VCO_2 is derived from the formula RQ × VO_2 = VCO_2. VO_2 implies oxygen consumption as measured by the equipment using O_2 sensors and the respiratory quotient for mixed diet is considered as 0.85.[17]

Statistical analysis

Statistical analyses were carried out using the SPSS (Chicago, IL, USA). All outcome variables were tested for normality. Differences in means were tested using a *t*-test for parametric data. Correlation analysis was performed using Pearson's coefficient. Independent *t*-test was used to assess anthropometric, RMR and body composition differences in adolescents and youth with T1D (<5 years disease duration) as compared to those with >5 years disease duration. For testing relationships between dependent variables and continuous predictors, linear regression was performed. Independent variables in the models were LBM percentage, energy intake/kg body weight (kcal/kg), gender, IS (SEARCH) and age (replacement with diabetes duration yielded similar results); the dependent variable was the RMR adjusted for weight.[7] HbA1c was not added as it is included in the SEARCH equation for IS. *P*-values < 0.05 were considered significant. For the comparison of means between two independent groups, our sample size was sufficient to obtain a *post hoc* power of more than 0.8 with $\alpha = 0.05$ (G Power 3.1.9.4).

Ethical aspect

This study was approved by Ethics Commitee Jehangir Clinical Development Center Pvt. Ltd. on 07/08/2019. The study was conducted in accordance with the local legislation, institutional requirements and was in compliance with Declaration of Helsinki (1964). Informed consent was taken from the parents of all participants and informed consent/assent was taken from all participants as applicable.

Results

In total, 97 adolescents/youth with T1D (50 girls and 47 boys, 10 to 18.8 years) along with 95 age- and gender-matched healthy controls (48 girls and 47 boys, 10 to 18.9 years) were enrolled in the study. The mean age of the group with type 1 diabetes (14.4 ± 2.3 years), was like that of healthy controls (14.3 ± 2.3 years, $P > 0.05$). Of the subjects with T1D, 86 were on basal bolus regimen and 11 on split-mixed insulin. 65 subjects (67%) showed poor control of diabetes (HbA1c >9% [75 mmol/mol]).

Demographic and clinical differences of subjects are illustrated in Table 1. Adolescents with T1D were significantly shorter and had lower carbohydrate, protein, fat, and overall calorie intake as compared to healthy controls ($P < 0.05$). They also had a significantly higher RMR (both unadjusted and adjusted for body weight) and VO_2 than the controls ($P < 0.05$).

Boys had a higher LBM percentage (83.9 ± 5.6) as compared to girls (71.3 ± 8.5, $P = 0.001$), whereas girls had a significantly higher fat percentage (24.6 ± 8.6 vs. 11.5 ± 5.9 in boys; $P = 0.001$).

On performing correlation analysis, RMR adjusted for weight showed a positive correlation with LBM percentage ($P = 0.001$, Pearson's coefficient = 0.631, Figure 1), energy intake per kg body weight ($P = 0.001$, Pearson's coefficient = 0.549) and a negative correlation with disease duration (diabetic age) ($P = 0.03$, Pearson's coefficient r = -0.279, Figure 2). It also showed a negative correlation with advancing age. HbA1c demonstrated a significant positive correlation with RMR adjusted for weight ($P = 0.04$, Pearson's coefficient = 0.234),

Table 1: Characteristics of adolescents and youth with Type 1 diabetes and healthy controls in the study

Parameters	Type 1 DM (*n*=97)	Healthy controls (*n*=95)
Age (years)	14.4±2.3	14.2±2.3
Height (cm)	150.5±12.4	153.2±9.8
Weight (kg)	41±11.2	42.5±9.5
BMI	17.8±3	17.8±2.6
Height Z-score*	-0.7±1.1	-0.4±1.0
Weight Z-score	0.7±0.9	0.5±0.8
BMI Z-score	-0.5±0.8	-0.4±0.7
Measured RMR (kcal/day)*	1526±276	1140±206
RMR (adjusted for weight) (kcal/kg)*	38.9±8.6	27.8±6.5
RMR (adjusted for FFM) (kcal/kg)*	47.3±8.5	33.2±6.2
VO_2 (mL/min)*	216.9±45.2	163.5±29.5
Fat percentage	18.2±9.9	17.2±8.8
Fat percentage Z-score	-0.4±0.9	-0.5±0.8
LBM percentage	77.5±9.5	78.8±8.9
LBM percentage Z-score	0.45±0.9	0.63±0.9
FFM (kg)	33.1±8.1	34.9±7
Energy intake (kCal)*	1253.7±445.0	1856.7±650.5
Carbohydrate intake per kg body Weight*	4.8±1.9	6.8±2.5
Protein intake per kg body weight*	0.8±0.4	1.1±0.5
Fat intake per kg body weight*	0.9±0.4	1.4±0.7
Energy intake per kg body weight*	31.2±12.2	45.1±16.4

(RMR-resting metabolic rate, VO_2-volume of oxygen, LBM-lean body mass, BMI-body mass index, DM-diabetes mellitus, FFM-fat-free mass) (*level of significance $P<0.05$) (all values are expressed as mean±standard deviation)

whereas insulin sensitivity demonstrated a significant negative correlation ($P = 0.001$, Pearson's coefficient = 0.321). Linear regression indicated LBM to be an important predictor of RMR in T1D. On adjusting the RMR for weight, an increase of 0.5% in muscle mass increased RMR by 1 unit ($P < 0.05$). Higher energy intake/kg body weight was found to be positively associated with adjusted RMR. Male gender and higher IS tended towards significant negative association with adjusted RMR [Table 2].

Because disease duration (diabetic age) was negatively associated with RMR, we compared subjects with T1D based on disease duration [Table 3]. Those with a disease duration of <5 years showed a significantly higher RMR as compared to those with a disease duration >5 years. Subjects (<5 years disease duration) also showed a lower body fat and higher LBM percentage, higher energy and carbohydrate intake/kg body weight, and higher calculated IS.

Discussion

Our case-controlled study showed that adolescents with T1D had higher RMR (unadjusted and adjusted for weight) and oxygen consumption (VO_2) than healthy controls. Among patients with T1D, weight-adjusted RMR showed a positive correlation with LBM, and energy intake and a negative correlation with disease duration. Further, LBM was found to be an important predictor of RMR in these subjects. Similarly, higher energy intake/kg body weight was associated with a higher adjusted RMR. Male gender and higher IS showed a trend towards negative association with adjusted RMR. We also found that as age (and duration of diabetes) advanced, RMR adjusted for weight decreased, probably due to a reduction in LBM as documented in subjects with greater diabetes duration. Thus, apart from the known factors impacting RMR (LBM and energy intake), subjects with diabetes were more likely to have a higher RMR when they had a shorter disease duration and lower body fat percentage.

To the best of our knowledge, this is the first study to report RMR in adolescents with T1D. The handful of studies, published in subjects with diabetes are mainly in adults with type 2 diabetes (T2D).[18-20] A study conducted by Alawad *et al*., which evaluated RMR in obese adults with T2D and obese non-diabetic subjects reported a significant difference in RMR between the two study groups with higher RMR in T2D.[18] They also reported a reduction in resting energy expenditure following improvement in glycaemic control. In another study, Pima Indian patients with T2D were found to have a higher rate of energy expenditure.[19] Similar findings have been reported in a systematic review by Caron *et al*.[20] An increase in gluconeogenesis has been proposed as one of the reasons

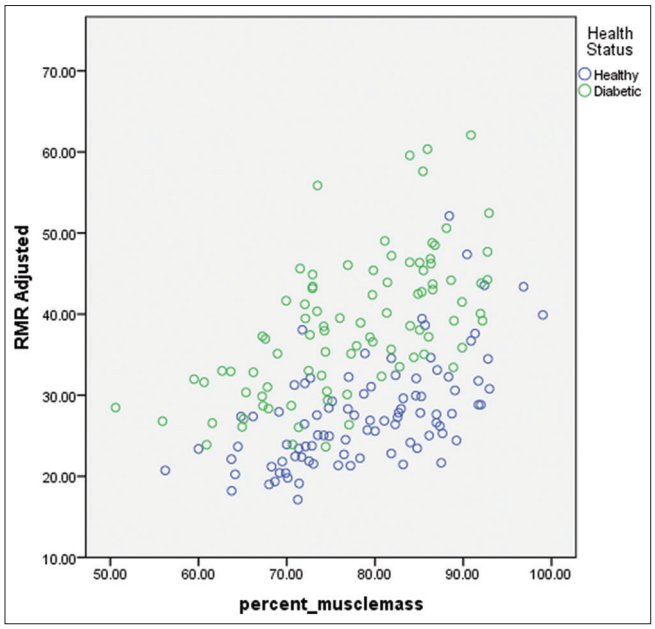

Figure 1: Association of RMR (adjusted for weight) with LBM percent among adolescents with type 1 diabetes and healthy controls

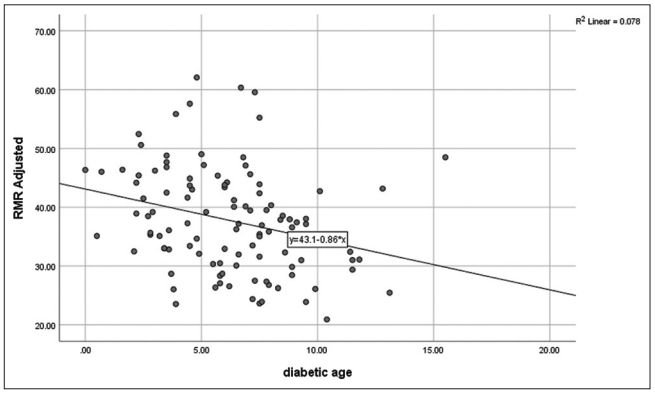

Figure 2: Association of RMR (adjusted for weight) with disease duration in adolescents and young adults with Type 1 diabetes

Table 2: Predictors of RMR (adjusted for weight) in adolescents and young adults with type 1 diabetes using linear regression model

	Beta	SE	*P*	CI (lower bound)	CI (upper bound)
Constant*	21.6	8.8	0.01	4.1	39.2
Male gender*	-3.0	1.6	0.06	-6.2	0.2
LBM percentage*	0.5	0.1	0.00	0.3	0.7
Calculated insulin sensitivity (SEARCH) above 5.485 mg/kg/min	-4.4	2.3	0.06	-9.0	0.2
Energy intake per kg body weight*	0.1	0.1	0.02	0.0	0.2
Age*	-1.4	0.3	0.00	-1.9	-0.8

* Level of significance *P*-value <0.05. SE-standard error, CI-confidence interval, HbA1c-glycosylated haemoglobin, LBM percentage-lean body mass percentage

Table 3: Anthropometric, RMR and body composition differences in adolescents and young adults with T1D (<5 years disease duration) as compared to those with >5 years disease duration

Parameters	Disease duration (<5 years) (*n*=38)	Disease duration (>5 years) (*n*=59)	*P*
Age (years)	13.8±2.1	14.7±2.3	0.059
Height Z-score	-0.7±1.3	-0.8±0.9	0.641
Weight Z-score	-0.8±0.9	-0.6±0.7	0.574
BMI Z-score	-0.6±0.7	-0.4±0.9	0.316
Measured RMR (kcal/day)	1528.1±299	1524.2±262.5	0.947
RMR (adjusted for weight) (kcal/kg)*	41.5±8.1	37.3±8.6	0.018
RMR (adjusted for FFM) (kcal/kg)*	49.5±8	45.9±8.6	0.048
VO_2 (mL/min)	213.7±55.3	218.9±37.7	0.583
HbA1c	10.1±1.6	10.6±1.9	0.791
Total daily dose of insulin (I.U.) per kg body weight	1.1±0.3	1.0±0.3	0.163
Fat percentage*	15.4±8.3	19.9±10.5	0.034
Fat percentage Z-score	-0.6±0.8	-0.3±1.0	0.080
LBM percentage*	80.3±8.3	75.6±9.9	0.023
LBM Z-score*	0.7±0.8	0.2±0.8	0.024
FFM (kg)	31.9±8.4	33.9±7.9	0.256
Energy (kcal)	1284.0±437.78	1193.1±433.7	0.322
Carbohydrate intake (g) per kg body weight*	5.5±2.1	4.5±1.7	0.013
Protein intake (g) per kg body weight	0.9±0.4	0.8±0.4	0.117
Fat intake (kg) per kg body weight	1.0±0.5	0.9±0.4	0.108
Energy intake (Kcal) per kg body weight*	35.6±13.1	29.2±11.6	0.015
Calculated insulin sensitivity (mg/kg/min) (SEARCH)*	9.5±1.8	8.5±2.4	0.037

BMI-body mass index, RMR-resting metabolic rate, VO_2-volume of oxygen, HbA1c-glycosylated haemoglobin, LBM-lean body mass, FFM-fat-free mass. *level of significance $P<0.05$) (all values are expressed as mean±standard deviation

for this finding.[21] Increased free fatty acid concentrations in patients with diabetes possibly contribute to an increased rate of gluconeogenesis and therefore to an increased rate of energy expenditure in these patients.[19]

Whole-body studies have demonstrated increases in both protein breakdown and synthesis in subjects with poorly controlled T1D or insulin deprivation. However, as the magnitude of the increase in protein breakdown is larger than that of the increase in protein synthesis, there is net protein loss that is associated with a higher rate of energy release and thus higher RMR in subjects with T1D.[22] This possibly explains the findings of low calorie and protein intake, yet high RMR in our study. Adolescents with T1D in our study with mean HbA1c of 9%, that is, who were poorly controlled had higher RMR as compared to healthy controls; our study subjects also had lesser LBM as compared to the healthy controls (possibly due to excess protein breakdown). Increased plasma glucagon levels in poorly controlled subjects with T1D is another reason postulated for the increase in RMR in these patients. Increased glucagon levels are likely to increase gluconeogenesis (a process that consumes a lot of energy) and leucine oxidation, thereby contributing to a hypermetabolic state and increased RMR in T1D.[23,24]

Our study revealed a significant negative correlation between RMR and diabetes disease duration. Also, advancing age (and thereby, diabetes duration) was negatively associated with RMR. This could be attributed to the decreased LBM in adolescents and young adults with disease duration >5 years observed in our cohort. A decrease in LBM with an increase in disease duration has also been demonstrated by Wierzbicka *et al*.[25] The reasons for decreased LBM with increased disease duration could be due to insulin deficiency and subsequent insulin-like growth factor-1 (IGF-1) reduction, hyperglycaemia-induced oxidative stress and accumulation of advanced glycation end-products (AGEs) that compromise collagen properties that can lead to decreased LBM and hence RMR in children with longer disease duration.[26,27]

Using linear regression analysis, we found that LBM played a significant role in predicting RMR in subjects with T1D. It is well documented that FFM contributes to about 70–80% variability in RMR in normal individuals. Similar findings have been demonstrated in a review by Cunningham *et al*., where a primary correlation between REE and FFM in subjects over a broad range of weights was confirmed.[28] The remaining 20–30% residual variability has been shown to be associated with age, body fat, body temperature and activation of the sympathetic nervous system.[29] The residual variability in RMR may also be explained by the composition of the FFM. FFM is composed of tissues characterised by different levels of energy expenditure per unit of mass. The energy expenditure of the visceral organs and the brain is roughly 1 MJ/kg/d, whereas for skeletal muscle (at rest) it is about 20 times lower.[30]

We found higher energy intake/kg body weight to be a positive predictor of RMR. This finding is in line with other studies, as observed from a review by Molé *et al*.[31] Following a higher

calorie intake, although initially, the metabolic rate increases transiently due to the need for transfer and storage of ingested nutrients, chronic overfeeding leads to increased RMR. This may also partly explain the higher RMR observed among our patients with a shorter duration of T1D after a higher energy intake.

Similar to our study, IR has been found to be a predictor of RMR in several studies.[10,32] A study by Drabsch *et al*. reported that insulin resistance was independently associated with a lower RMR in healthy adults. Various other studies have demonstrated a higher RMR in individuals with T2D.[18] These findings suggest that IR may contribute to a slower metabolism, which could potentially lead to weight gain and subsequent complications. It is important to note, however, that the relationship between IR and RMR is complex and may be influenced by other factors such as age, sex, and BC. Moreover, the cause–effect relationship may also be bidirectional, with lower RMR predisposing to the development of obesity, insulin resistance and T2D; further research is needed to fully understand the mechanisms underlying this association.[9]

The strength of our study is the novelty of studying RMR, BC and the factors (pertinent to the disease) affecting it in T1D. To the best of our knowledge, this is the first study describing RMR in youth with T1D and age- and gender-matched healthy controls. Our study also has an adequate sample size as compared to previous studies and focuses specifically on RMR. Our study is limited by the fact that the COSMED instrument only measures VO_2 and not VCO_2 (thus, there is an assumption about the respiratory exchange ratio).[33] This assumed ratio may not be correct for clinical populations with metabolic disorders as previous studies report that subjects with T1D have higher fat oxidation than control groups.[34] There are thus no sufficient data to factor in the disease status in the calculation of VCO_2. Further limitations are that ours was a cross-sectional design and the data were from a single centre and may not be generalisable. More studies on adolescents and young adults with T1D are required to validate the findings of our study.

Conclusion

Indian adolescents with type 1 diabetes had a higher resting metabolic rate as compared to healthy controls. LBM and energy intake were found to be important positive predictors of RMR in adolescents and young adults with T1D, whereas advancing age and disease duration were found to be negative predictors. Reduction in RMR with advancing age/disease duration may predispose to adiposity and subsequent double diabetes. Further long-term studies are required to assess the changing trends in RMR and body composition with the evolution of the disease.

There is increasing evidence of the occurrence of insulin resistance (IR) in patients with T1D, the pathogenesis of which is multifactorial; obesity is a major determinant of IR in T1D. Although the HOMA IR gives an estimate of IR, it cannot be utilised in T1D due to negligible endogenous insulin production, and the influence of exogenously administered insulin. Further, although the hyperinsulinaemic-euglycaemic clamp studies are the gold standard for the diagnosis of IR in T1D, they are cumbersome.

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Authors' contribution

MK conceptualised and designed the study, SB and KG contributed to the acquisition of data, and analysis and interpretation of data. SM, NS, SK, AK, KG and VK conceptualised, contributed to analysis and interpretation of data. All authors contributed to manuscript writing and checking. All authors have accepted responsibility for the entire content of this submitted manuscript and approved submission.

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Conflicts of interest

There are no conflicts of interest.

Data availability statement

Data supporting the findings of this study is available with the corresponding author.

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