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Triglyceride-glucose index in adolescents with type 1 diabetes mellitus

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ABSTRACT

Background and Aim: Even though HbA1c can be obtained easily and accurately by blood test, the cost may limit its availability for some patients and their proper follow-up. The triglyceride-glucose index has been shown to have an association with HbA1c in other populations, but it hasn't been studied in adolescents with T1DM yet. The aim of this study is to assess the association of TyG index with glycaemic control in adolescents with T1DM.
Methods: This cross-sectional study included a sample of 36 adolescents (50% female) from the paediatric unit of the San Juan Hospital in Alicante (Spain). Data on sociodemographics, growth parameters, glycaemic control, and blood tests results were collected after routine visits.
Results: A higher TyG index was statistically associated with a higher BMI, percentile and z-score, a higher triglyceride, HbA1c and glucose levels and with the triglycerides/HDL, the total cholesterol/HDL, the TyG-BMI and the TyG-waist circumference indexes.
Conclusion: The TyG index is a simple and non-invasive biomarker that could serve as a valuable adjunct to HbA1c monitoring in adolescents with T1DM. It may have a potential utility as a screening tool for early identification of patients at risk for developing metabolic complications such as insulin resistance and dyslipidemia.

1. Introduction

Diabetes mellitus is a complex metabolic disorder characterized by chronic hyperglycaemia resulting from defects in insulin secretion, insulin action, or both [1]. Specifically, type 1 diabetes mellitus (T1DM) is characterized by the destruction of the ß-cells, usually by an autoimmune process, resulting in loss of endogenous insulin production [1]. According to International Society for Paediatric and Adolescence Diabetes (ISPAD), in terms of prevalence, predictions for 2040, based on findings in 2021, include an increase in prevalent cases from 8.4 million individuals worldwide to 13.5–17.4 million [1].

As is the case with other pathologies, adolescents with T1DM have different health needs than younger children or adults, as this is a transitional phase of development between them [1] ranging from 10 to 19 years of age, according to the World Health Organisation (WHO) [2]. As patients' energy, nutritional needs and body composition change during this stage of life, close clinical monitoring [3] is necessary to assess and monitor their health status in order to facilitate early intervention and improve prognosis [3,4].

The energy and nutritional needs and body composition of adolescents change at this stage of life [3]. Therefore, it is important to keep in mind that, in parallel with the recent increase in prevalence of T1DM, there has been a concerning increase in obesity in T1DM adolescent patients [5,6]. This may be due to the use of exogenous insulin and intensive insulin therapy among other causes like fear of hypoglycaemia and related decrease in physical activity, and psychological factors such as emotional eating or binge eating [7]. The interaction between overweight or obesity and T1DM seems to be bidirectional. Weight gain is a side effect of T1DM treatment and is the risk factor for its development [7,8]. In both cases, the two pathologies seem to be associated, which is relevant when considering the importance of body mass index (BMI), z-score and percentile in routine consultations with adolescents according to their age and gender [9,10].

In terms of glycaemic control, glycosylated haemoglobin (HbA1c) is

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a well-established biomarker and currently the gold standard parameter in the assessment of glycaemic control in diabetes mellitus, as it is highly associated with the risk of chronic vascular complications. According to the ISPAD, the recommended HbA1c target is below 6.5 % for adolescents who have access to advanced diabetes technologies such as continuous glucose monitoring (CGM) and automated insulin delivery [11]. Although this more stringent target should be encouraged for all young people with diabetes when safely achievable, in cases where access to these technologies is limited, the HbA1c target remains $\leq$ 7.0 % [11].

While HbA1c is a widely used and valuable tool for monitoring long-term blood sugar and it offers valuable insights into average glucose levels over the past 2–3 months, it should be noted that HbA1c may not fully capture the nuances of daily glucose fluctuations [12–14]. Although these short-term variations can influence health outcomes, HbA1c provides a broader perspective on overall glycaemic control in routine follow-up consultations of patients with T1DM [12–14]. Moreover, even though it can be obtained easily and accurately by blood test [11,15], the cost associated with HbA1c testing may restrict its routine inclusion in laboratory panels, which may limit its availability for some patients and their proper follow-up, reducing the effectiveness of health intervention [16,17]. In this regard, a Spanish study found that providing all necessary HbA1c tests to diabetic patients could have incurred a cost of approximately €5.5 million, emphasizing the financial implications of ensuring adequate testing and follow-up [16].

Furthermore, there are other indicators such as the coefficient of variation (CV) or the time in range (TIR) that also indicate better or worse diabetes management [11,18]. The CV, a measure of the dispersion of glucose values, and the TIR, representing the percentage of time spent within a target glucose range (70–180 mg/dL or 3.9–10.0 mmol/L), are particularly useful in evaluating glycaemic variability and overall control [11]. While these parameters can be calculated from CGM data, their clinical interpretation is essential for optimizing treatment strategies and preventing complications [11,18].. Notably, the adoption of CGM and other advanced technologies, although beneficial, can significantly impact healthcare costs, accounting for up to 32 % of the total annual cost for pediatric patients with T1DM in Spain [19]. The American Diabetes Association (ADA) recommends using the CV as the standard deviation adjusted by the 24-hour mean glucose level [18,20] and defines TIR as the percentage of time spent within the target glucose range over a 24-hour period [20].

Fortunately, there are other biochemical indicators that have been shown to correlate positively with HbA1c and are obtained from less expensive parameters commonly present in routine blood tests performed on patients. One of these is the triglyceride-glucose index (TyG index), which has been shown to have a statistically significant association with HbA1c in adult patients with T1DM [21], type 2 diabetes mellitus (T2DM) [22–25] and with metabolic syndrome (MS) [26,27] as it is considered a biomarker of insulin resistance [21,26,27]. Besides, while HbA1c testing requires an additional assay, increasing laboratory expenses, the triglyceride-glucose index can be calculated from routine fasting glucose and triglyceride measurements. Thus, incorporating the TyG index does not necessitate additional laboratory work or incur extra costs. However, although it has been shown to be an insulin resistance marker in the paediatric obese population [28], its association in adolescents with T1DM has not been studied yet. Therefore, the aim of this study is to assess the association of TyG index with glycaemic control in adolescents with T1DM.

2. Methods

2.1. Design

This is a cross-sectional study carried out in the paediatric unit of the San Juan Hospital (Alicante, Spain), from July 2022 to April 2024. Data were collected from a sample of adolescents with T1DM after their routine consultations. The study population was selected by non-probabilistic sampling method and participants were included if they were 10–16 years old and diagnosed with T1DM, regardless of CGM use. Participants were excluded if they were currently hospitalized. Female participants of childbearing potential were also excluded if pregnant, as pregnancy can significantly influence biochemical parameters off interest in this study like blood lipids and glucose [29–31].The sample size calculation was performed with RStudio software (version 3.15.0, RStudio Inc., Boston, MA, USA). The significance level was set a priori at $p = 0.05$. The standard deviation (SD) for HbA1c percentage was determined from previous studies (SD = 1.26) [32]. Based on this methodology, the minimum required sample size was 36 participants, with an estimated error (d) of 0.41 for HbA1c percentage within a 95 % confidence interval (CI). The study aimed for a statistical power greater than 0.80, achieving a calculated power of 0.96, which is considered high. In addition, the study design as well as the development of the manuscript followed the STROBE statement [33].

2.2. Ethics

The study was conducted in accordance with the Declaration of Helsinki. Ethical approvals were obtained from the Research Ethics Committee of San Juan Hospital (committee no. 22/038). Both participants and their legal guardians were informed of the objective of the study and legal guardians signed an informed consent form.

2.3. Data collection

All variables were collected directly from the patients' medical records. The biochemical parameters of interest were collected from most recent blood tests, obtained within a 1-to-6-month period coinciding with their last routine paediatric consultation.

2.4. Variables

2.4.1. Outcome Variable: TyG index

The TyG index was calculated as Ln[fasting triglycerides (mg/dl) x fasting glucose (mg/dl)/2] [34].

2.4.2. Predictive variables

Clinical Variables.

The BMI, percentile and z-score (both based on BMI for age) of each patient were calculated using the WHO AntroPlus software [35] and the variables age, date of birth, sex, weight and heigh. Weight was categorized as follows: underweight if percentile was less than 5, a normal weight percentile of between 5 and less than 85, an overweight percentile of between 85 and less than 95 and an obesity percentile of 95 or more [36]. Similarly, an underweight z-score of less than −2, a normal weight z-score of between −2 and 0.99, an overweight z-score of between 1 and 1.99 and an obesity z-score of more than 2 were assumed [37].

Glycaemic control was assessed using the CV and TIR, both calculated as the mean of the previous 14 days of CGM data. A normal CV was defined as $\leq$ 36 % and a normal TIR was defined $>$ 80 % to achieve an optimal HbA1c target of $\leq$ 6.5 % [11].

The TyG-BMI was calculated as TyG index $\times$ BMI and the TyG-Waist circumference (TyG-WC) was calculated as TyG index $\times$ WC (cm) [38].

Biochemical Variables.

The following biochemical variables were obtained by analysis of a blood sample collected as part of the routine clinical follow-up: Glucose (mg/dL), HbA1c (%), total cholesterol (mg/dL), HDL cholesterol (mg/dL), LDL cholesterol (mg/dL) and triglycerides (mg/dL). From these parameters some indexes were calculated, such as the total cholesterol/HDL index, the LDL/HDL index and the triglycerides/HDL index. Of the entire sample, there were some cases where lipid parameters did not appear in the blood tests. For this reason, one data for total cholesterol,

one data for HDL cholesterol and five data for LDL cholesterol were missing.

2.5. Statistical Analyses

A descriptive analysis of the sample was carried out by describing the percentages for the whole sample and for the groups of female adolescents and male adolescents separately. The database was analysed using SPSS Statistics software for Windows version 28.0 (IBM, Spain). Correlations between outcome and predictable variables were analysed using Pearson or Spearman tests, depending on the normality assessed by the Shapiro-Wilk test. The statistical significance of the results was assumed as high ($p < 0.001$) and medium ($0.001 < p < 0.05$).

3. Results

3.1. Sample characteristics

Table 1 shows the sample's socio-demographic and clinical characteristics. A total of 36 participants were recruited in the study and 50 % of whom were female adolescents. Of the total sample, 19.4 % had between 10 to 11 years old, 38.9 % had between 12 to 13 years old and 41.7 % had between 14 to 16 years old. Most of the study participants were using a CGM (83.3 %) and had CV and TIR values that corresponded to uncontrolled glycaemia (64.3 % and 73.4 %, respectively).

Table 1
Adolescents with Type 1 Diabetes Mellitus' Socio-Demographic and Clinical Characteristics Including Age, Gender, Use of Continuous Glucose Monitor, Coefficient of Variation (CV), Time in Range (TIR), HbA1c, BMI, Percentile and Z-Score.

	Whole sample	Male adolescents	Female adolescents
Gender	36 (100 %)	18 (50 %)	18 (50 %)
Age	36 (100 %)	18 (50 %)	18 (50 %)
10 to 11 years old	7 (19.4 %)	2 (11.1 %)	5 (27.8 %)
12 to 13 years old	14 (38.9 %)	9 (50 %)	5 (27.8 %)
14 to 16 years old	15 (41.7 %)	7 (38.9 %)	8 (44.4 %)
Use of Continuous Glucose Monitor	36 (100 %)	18 (50 %)	18 (50 %)
Yes	30 (83.3 %)	16 (53.3 %)	14 (46.6 %)
No	6 (16.7 %)	2 (33.3 %)	4 (66.6 %)
CV	28 (77.8 %)	15 (53.6 %)	13 (46.4 %)
≤ 36 % (controlled)	10 (35.7 %)	3 (20 %)	7 (53.8 %)
>36 % (not controlled)	18 (64.3 %)	12 (80 %)	6 (46.2 %)
TIR	30 (83.4 %)	16 (53.3 %)	14 (46.6 %)
≥ 80 % (controlled)	8(26.6 %)	3 (18.7 %)	5 (35.7 %)
< 80 % (not controlled)	22 (73.4 %)	13 (81.3 %)	9 (64.3 %)
HbA1c	35 (97.3 %)	17 (48.6 %)	18 (51.4 %)
≤ 6.5 % (controlled)	5 (14.3 %)	3 (17.6 %)	2 (11.1 %)
≥ 6.6 % (not controlled)	30 (85.7 %)	14 (82.4 %)	16 (88.9 %)
BMI	36 (100 %)	18 (50 %)	18 (50 %)
<18 Kg/m^2 (underweight)	6 (16.7 %)	3 (16.7 %)	3 (16.7 %)
18 to 24.9 Kg/m^2 (normal weight)	22 (61.1 %)	11 (61.1 %)	11 (61.1 %)
25 to 29.9 Kg/m^2 (overweight)	6 (16.7 %)	4 (22.2 %)	2 (11.1 %)
> 30 Kg/m^2 (obesity)	2 (5.6 %)	0 (0 %)	2 (11.1 %)
Percentile (BMI for age)	36 (100 %)	18 (50 %)	18 (50 %)
< P5 (underweight)	2 (5.6 %)	2 (11.1 %)	0 (0 %)
P5 to P84.9 (normal weight)	18 (50 %)	7 (38.9 %)	11 (61.1 %)
P85 to P94.9 (overweight)	9 (25 %)	6 (33.3 %)	3 (16.7 %)
≥P95 (obesity)	7 (19.4 %)	3 (16.7 %)	4 (22.2 %)
Z-score (BMI for age)	36 (100 %)	18 (50 %)	18 (50 %)
< −2,00 (underweight)	2 (5.6 %)	2 (11.1 %)	0 (0 %)
−2,00 to + 0,99 (normal weight)	18 (50 %)	7 (38.9 %)	11 (61.1 %)
+1,00 to 1,99 (overweight)	9 (25 %)	6 (33.3 %)	3 (16.7 %)
≥ 2,00 (obesity)	7 (19.4)	3 (16.7 %)	4 (22.2 %)

CV: Coefficient of variation; TIR: Time in range; HbA1c: Glycosylated haemoglobin; BMI: Body mass index.

These findings are consistent with HbA1c levels, as the majority of the sample (85.7 %) presented values outside the target range.

At this point, male adolescents were shown to have worse controlled glycaemia reflected in CV (80 % in male adolescents and 46.4 % in female adolescents) and TIR (81.3 % in male adolescents and 64.3 % in female adolescents) values. Regarding HbA1c, the majority of both male and female adolescents showed similar values outside the target range (82.4 % in male adolescents and 88.9 % in female adolescents).

In terms of growth and body mass, BMI showed that most of the participants had normal weight (61.1 %) and the same was reflected in the percentile and z-score values based on BMI for age (50 % in both cases). Nevertheless, both indicators found a higher proportion of overweight (25 %) and obesity (19,4%) in the whole sample compared to BMI (only 16.7 % of overweight and 5.6 % of obesity).

3.2. Biomarker analysis

The results obtained from the correlation analysis between biomarkers and TyG index are shown in Table 2. Both in the whole sample and in the groups of male adolescents and female adolescents separately, a higher TyG index was statistically associated with a higher percentile, a higher triglyceride, HbA1c and glucose levels and with the triglycerides/HDL and the TyG-BMI indexes.

Moreover, TyG index was also associated with a higher BMI and z-score in the whole sample and the male adolescents' group. In the case of total cholesterol/HDL index, an association was found in the whole sample and in the female adolescents' group. In addition, the TyG-WC index showed to be positively associated in the whole sample and to have a tendency to correlate in the female adolescents' group. Finally, the variables that seem to be close to correlate, also positively, are CV (in the whole sample) and LDL cholesterol (in the male adolescents' group).

4. Discussion

This study aimed to investigate the association between the TyG index and glycaemic control in adolescents with T1DM. Our findings revealed a significant positive correlation between the TyG index and HbA1c, suggesting that higher TyG values are associated with poorer glycaemic control. Although we found a trend towards a positive correlation between the TyG index and CV, this relationship did not reach statistical significance. Given the sample size of our study, it is possible that this association may become more apparent with a larger cohort.

Although CV and TIR are commonly used measures of glycaemic variability [39,40], it is important to note that their use, although informative, are subject to certain constraints [40,41]. Firstly, both CV and TIR calculations rely on CGM data, which is not universally available to all individuals with T1DM. Although CGM usage is becoming more widespread, there remains a subset of patients who do not have access to or choose not to use these devices. Consequently, the generalizability of findings based solely on CGM data may be limited. Secondly, the accuracy and reliability of CV and TIR estimates are contingent upon consistent and prolonged CGM usage. Periods of sensor disconnection or inadequate wear time can lead to gaps in data collection, potentially underestimating or overestimating the true extent of glycaemic variability. Furthermore, factors such as sensor calibration errors and individual variations in CGM sensor performance can introduce additional variability into the data [40,41]. Notably, the MARD (Mean Absolute Relative Difference) index, a measure of sensor reliability, differs between some of the most commonly used CGM sensors. These differences in MARD index [42,43] can influence the reliability of TIR and CV measurements in evaluating glycaemic variability.

In addition, a significant positive correlation was observed between the TyG index and various markers of adiposity, including BMI, BMI percentile, and BMI z-score. This association suggests that a higher TyG index, indicative of increased insulin resistance, is linked to greater adiposity in adolescents with T1DM.

Table 2
TyG Index Correlations in Adolescents with Type 1 Diabetes Mellitus.

Predictive variable	Whole sample	p-value	Male adolescents	p-value	Female adolescents	p-value
Age	0.185 (n = 36)	0.281	0.200 (n = 18)	0.425	0.176 (n = 18)	0.485
CV	0.336 (n = 28)	0.080	0.360 (n = 15)	0.187	0.258 (n = 13)	0.395
TIR	−0.225 (n = 30)	0.232	−0.070 (n = 16)	0.794	−0.329 (n = 14)	0.250
HbA1c	0.680 (n = 35)	<0.001**	0.593 (n = 17)	0.012*	0.749 (n = 18)	0.001**
BMI	0.445 (n = 36)	0.007**	0.548 (n = 18)	0.018*	0.394 (n = 18)	0.106
Percentile	0.503 (n = 36)	0.002**	0.555 (n = 18)	0.017*	0.459 (n = 18)	0.055*
Z-score	0.422 (n = 36)	0.010*	0.514 (n = 18)	0.029*	0.383 (n = 18)	0.117
Glucose	0.744 (n = 36)	<0.001**	0.658 (n = 18)	0.003**	0.763 (n = 18)	<0.001**
Triglycerides	0.680 (n = 36)	<0.001**	0.621 (n = 18)	0.006**	0.795 (n = 18)	<0.001**
Total Cholesterol	0.020 (n = 35)	0.911	−0.377 (n = 17)	0.136	0.289 (n = 18)	0.245
HDL Cholesterol	−0.244 (n = 35)	0.158	−0.237 (n = 17)	0.359	−0.244 (n = 18)	0.330
LDL Cholesterol	0.047 (n = 31)	0.802	−0.507 (n = 17)	0.053*	0.239 (n = 16)	0.374
LDL/HDL Index	0.150 (n = 33)	0.406	−0.195 (n = 16)	0.469	0.346 (n = 17)	0.173
Tot.Cholesterol/HDL Index	0.394 (n = 35)	0.019*	0.039 (n = 17)	0.882	0.586 (n = 18)	0.011*
Triglycerides/HDL Index	0.656 (n = 35)	<0.001**	0.568 (n = 18)	0.017*	0.696 (n = 18)	0.001**
TyG-BMI Index	0.681 (n = 36)	<0.001**	0.746 (n = 18)	<0.001**	0.655 (n = 18)	0.003**

CV: Coefficient of variation; TIR: Time in range; HbA1c: Glycosylated haemoglobin; BMI: Body mass index; *p < 0.05; **p < 0.01.

Previous studies have established the triglycerides/HDL index as a potential indicator of insulin resistance in adults (25), obese children (36), adolescents without diabetes (37), and individuals with type 2 diabetes mellitus (T2DM) (24). Additionally, this ratio has been recognized as a biomarker of cardiovascular risk in adolescent population (37, 38). Our findings in adolescents with T1DM further support these associations, as the triglycerides/HDL index was significantly correlated with glycosylated haemoglobin, total cholesterol/HDL index, BMI, and the TyG index. Moreover, the significant correlations observed between the TyG index and various metabolic syndrome indexes, including the total cholesterol/HDL, triglycerides/HDL, and TyG-BMI, reinforce the utility of the TyG index as a marker of metabolic dysregulation in this population. Consequently, both the triglycerides/HDL and TyG indexes may be used interchangeably to assess glycaemic control and cardiovascular risk in adolescent patients with T1DM.

It is worth noting that the TyG-waist circumference index has also been proposed as a potential marker of metabolic syndrome risk and insulin resistance in T2DM [44,45] and may provide further insights into the relationship between central adiposity and insulin resistance in adolescents with T1DM. Future studies should explore the clinical utility of this composite index in predicting metabolic complications in adolescents with T1DM.

Our findings support the hypothesis that the TyG index is a useful, simple and inexpensive biomarker for assessing insulin resistance and glycaemic control in adolescents with T1DM. The strong associations observed between the TyG index and glycaemic control, lipid profile, and anthropometric measures like BMI, BMI percentile and BMI z-score highlight the need for comprehensive metabolic assessments in adolescents with T1DM. Early identification of insulin resistance or poorer glycaemic control by using the TyG index may enable targeted interventions to improve glycaemic control and reduce the long-term comorbidity in adolescents with T1DM, as is the case in adults with T2DM, where al increased TyG index has already been shown to be an independent risk factor for diabetic nephropathy [24].

It is interesting to note that a previous study proposed cut-off points for the TyG index in Brazilian adolescents without diabetes to determine the presence of metabolic syndrome [46]. According to the proposed cut-off points (7.91 for male adolescents and 7.94 for female adolescents), in our sample three quarters of the participants were above them, which can be explained by the metabolic dysregulation of diabetes itself. However, another study in adults, also without diabetes and aiming to determine the presence of metabolic syndrome, proposed different cut-off points [47]. In this case, unlike the previous study, the cut-off point for men was higher than that proposed for women (8.8 and 8.7, respectively). Therefore, this suggests that it may be necessary to adjust the cut-off points of the TyG index for specific populations, such as adolescents with T1DM, differentiating by sex and age.

It is important to acknowledge several limitations of this study. First, the cross-sectional design limits our ability to establish causality. Longitudinal studies are needed to determine whether changes in the TyG index precede or follow changes in glycaemic control. Second, the relatively small sample size, a common limitation in studies involving adolescent T1DM population [48–50], may have limited our ability to detect smaller effect sizes and generalize our findings, but a significant sample in this type of population was used according to the statistical principles applied. Future studies with larger sample sizes are needed to confirm our findings and to explore the temporal relationship between the TyG index and the development of long-term complications in T1DM. Lastly, future research should explore the factors that influence the TyG index in adolescents with T1DM, such as genetic, environmental, and lifestyle factors. Additionally, studies investigating the impact of interventions aimed at improving insulin sensitivity, such as lifestyle modifications and pharmacotherapy, on the TyG index and glycaemic control would be valuable.

5. Conclusion

Our findings highlight the potential utility of the TyG index as a simple and non-invasive biomarker that could serve as a valuable adjunct to traditional HbA1c monitoring in adolescents with T1DM. Given its association with adiposity, insulin resistance and glycaemic control, the TyG index provides additional insights into the metabolic health of these patients and may have a potential clinical utility as a screening tool for early identification of adolescents with T1DM at risk for developing metabolic complications. Moreover, its calculation relies on readily available and cost-effective biochemical parameters, making it a feasible option for routine monitoring, especially in settings where HbA1c testing may be limited. Further research is warranted to explore the potential clinical utility of the TyG index in predicting long-term complications and guiding individualized treatment strategies for adolescents with T1DM.

6. Declaration of generative AI in scientific writing

The authors declare that no artificial intelligence was used during the study.

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The authors declare that no funding was received for this study.

CRediT authorship contribution statement

Marta García-Poblet: Writing – original draft, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Ana Pilar Nso-Roca:** Writing – review & editing, Resources, Methodology, Investigation, Data curation, Conceptualization. **José Miguel Martínez-Sanz:** Writing – review & editing, Validation, Supervision, Project administration, Methodology, Investigation, Conceptualization. **Isabel Sospedra:** Writing – review & editing, Validation, Supervision, Project administration, Methodology, Investigation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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