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CORRELATION BETWEEN CONTINUOUS GLUCOSE MONITORING PARAMETERS, THYROID HORMONES, AND LIPID STATUS IN PEDIATRIC TYPE 1 DIABETES: INSIGHTS FROM A THREE-MONTH STUDY

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ABSTRACT

Introduction: This study investigates the impact of sensor-augmented insulin pump therapy on thyroid-stimulating hormone (TSH), lipid profile, and glucose metabolism parameters in children with type 1 diabetes mellitus (T1DM) over a three-month period. **Methods:** A cohort of pediatric patients with T1DM undergoing sensor-augmented insulin pump therapy was monitored for changes in TSH, lipid profile, and continuous glucose monitoring parameters. Pearson correlation coefficients were calculated to assess associations between variables, and t-tests for paired samples were conducted to evaluate changes over time. **Results:** Our findings reveal a significant association between sensor-augmented insulin pump therapy and increases in TSH and total cholesterol, particularly in patients with initial HbA1c levels below 7.00%. Triglycerides exhibited significant correlations with time spent in normoglycemia and hyperglycemia, suggesting a link between glycemic control and lipid metabolism. Notably, thyroid hormones demonstrated associations with glucose control parameters, indicating potential interplay between thyroid function and glucose metabolism. **Conclusion:** These results underscore the importance of comprehensive metabolic monitoring in pediatric T1DM management, incorporating lipid status and thyroid function assessments alongside continuous glucose monitoring. Further research is warranted to elucidate these relationships and optimize metabolic control strategies in pediatric T1DM patients.

KEYWORDS: Type 1 diabetes mellitus, sensor-augmented insulin pump therapy, thyroid-stimulating hormone, lipid profile, continuous glucose monitoring, pediatric population.

INTRODUCTION

Type 1 diabetes mellitus (T1DM) comprises 5-10% of total diabetes cases and primarily afflicts children, representing the most prevalent endocrine disorder in pediatric populations.^[1] The global incidence of T1DM is increasing, with projections indicating a rise of 100,000 new cases worldwide by 2050.^[2] Concurrently, thyroid diseases represent the second most prevalent group of endocrine disorders.^[3] It is widely acknowledged that children with T1DM face an elevated risk of developing additional endocrine disorders, including Hashimoto's thyroiditis or celiac disease.^[4] This co-occurrence exacerbates metabolic dysregulation, particularly concerning in pediatric patients.

T1DM is characterized by autoimmune destruction of pancreatic beta cells, resulting in insulin deficiency.^[5] Biomarkers indicative of T1DM onset include islet cell antibodies (ICA), insulinoma-associated antigen-2 antibodies (IA2), glutamic acid decarboxylase antibodies

(GAD), and insulin autoantibodies (IAA). Similarly, autoimmune thyroiditis is identified by the presence of thyroid-stimulating hormone receptor antibodies (TSH-R-Ab), thyroid-stimulating antibodies (TSAb) in Graves' disease, or thyroid peroxidase antibodies (TPO) in Hashimoto's thyroiditis.^[6] Data indicate that 25% of adolescents with T1DM exhibit antibodies associated with autoimmune thyroiditis, suggesting a predisposition to subsequent multiendocrine disorders in this patient cohort.^[7] While this concurrent antibody presence is presumed to be genetically predisposed, the specific gene responsible for both diseases remain unidentified.^[8]

Thyroid hormones exert influence on glucose homeostasis through various mechanisms.^[9] Animal studies have elucidated the presence of thyroid hormone receptors on neonatal pancreatic beta cells. These hormones facilitate glucose absorption by enhancing gastrointestinal motility and stimulate hepatic glucose production by upregulating GLUT2 transporters in the

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liver.^[10] Furthermore, they directly promote insulin secretion and glucagon release, while in adipose tissue, they induce lipolysis, releasing free fatty acids that stimulate hepatic gluconeogenesis. Given these multifaceted effects, it is evident that thyroid hormones significantly impact glucose metabolism and may influence other hormonal axes as well.^[11]

Individuals with T1DM commonly exhibit dyslipidemia^[12], which increases the risk of cardiovascular diseases, the leading cause of mortality globally.^[13] Therefore, regular screening for dyslipidemia in children with T1DM is imperative to mitigate cardiovascular risk factors.

There is a dearth of studies examining the correlation between glucose metabolism, thvroid hormone concentrations, and cholesterol levels in pediatric populations, particularly those incorporating continuous glucose monitoring (CGM). CGM has become indispensable for managing T1DM in children, introducing novel parameters for assessing metabolic control, such as Time in Range (TIR).^[14] While the association between TIR and conventional parameters like glycated hemoglobin (HbA1c) has been extensively investigated^[15], its correlation with other laboratorymeasured metabolic parameters, such as cholesterol or thyroid hormones, remains inadequately explored. Therefore, our study aimed to investigate the impact of CGM and parameters derived from ambulatory glucose profiles on laboratory-measured thyroid hormones and lipids in children and adolescents, seeking to elucidate any existing dependencies between these parameters.

MATERIALS AND METHODS

The study was conducted at the Pediatric Clinic of the University Clinical Center of the Republic of Srpska in Banja Luka from January to July 2023. Participants were selected through random sampling, where every fifth patient who met the inclusion criteria and attended the clinic's outpatient department was informed about the study and offered participation. Inclusion criteria included age over 8 years, willingness to participate in the study, and duration of diabetes mellitus longer than one year. The exclusion criterion was a duration of diabetes mellitus less than one year. All participants or their parents/guardians were provided with study requirements and required to sign informed consent forms.

As per the study protocol, all participants were required to use an insulin pump connected to continuous glucose monitoring (CGM) for the next three months (90 days), regardless of whether they had previously used these technologies, and to have the suspend-before-low option enabled. They were also required to attend regular follow-up appointments. According to the research protocol, participants were instructed to record their activities for discussion of glucose levels during followup visits with the responsible healthcare provider. The upper glucose threshold for alarm activation was set at 10.0 mmol/L, and the lower threshold was set at 3.9 mmol/L. These thresholds remained unchanged, despite participants reporting during follow-up visits that the suspend-before-low option was triggering at higher glucose values than expected.

All diagnostic analyses were performed in accordance with the Helsinki Declaration recommendations at the reference laboratory within the institution, and the Ethical committee of the University clinical center of the Republic of Srpska approved the research. At the beginning of the study, laboratory tests (HbA1c, TSH, FT4, TPO antibodies, total cholesterol, LDL, HDL, triglycerides) were conducted, and anthropometric measurements (height, weight) were taken. The same analyses were repeated after three months. Regular follow-up appointments with counseling sessions for study participants were scheduled at 7, 14, 30, 60, and 90 days, during which dietary advice was provided, and insulin therapy was adjusted as needed.

STATISTICAL ANALYSIS

Numerical variables were described using measures of central tendency, including mean and standard deviation, as well as minimum and maximum values. Categorical variables were described using frequencies (%) of the total sample. IBM SPSS 22 statistical software was employed for data processing. Pearson's correlation coefficient was utilized as a measure of dependency between numerical variables, while the Chi-square test was employed for categorical variables. The dependency of numerical variables over time periods was assessed using paired samples t-tests. Linear and binary regression models were constructed based on the category of the dependent variable under investigation. Parameters obtained through CGM served as independent variables in our sample, with reference values derived from the Consensus on CGM use.^[10,11] Laboratory analyses were performed in an accredited standardized laboratory within our clinical center, which prescribed and provided reference values for the laboratory parameters analyzed.

RESULTS

Out of 35 participants who initiated the study, 30 completed it, with 14 (46.7%) being boys. Five participants did not adhere to the conditions outlined in the informed consent. The average age of the participants was 14.90 ± 2.88 years, with an average duration of diabetes mellitus of 7.83 ± 4.76 years. Among these participants, only 2 (6.7%) were diagnosed with celiac disease in addition to type 1 diabetes mellitus. Laboratory analyses and anthropometric measurements were conducted at the beginning and after 90 days, and the values are presented in Table 1.

| Variable | Baseline | 3 moths later – end of study |
|-------------------|------------------|------------------------------|
| BMI | 20.80±3.76 | 20.94±3.30 |
| HbA1c | 7.17±0.92 | 7.31±0.74 |
| Total cholesterol | 4.00±0.82 | 4.19±0.88 |
| HDL | 1.40 ± 0.32 | 1.41±0.32 |
| LDL | 2.72 ± 0.82 | 2.64±1.35 |
| Triglycerides | 0.71±0.27 | 0.78±0.35 |
| TSH | 2.22±0.87 | 2.69±1.88 |
| FT4 | 15.09 ± 2.10 | 14.42±1.55 |
| | | |

| Table 1: Values of the | variables at the begining | (baseline) and three moonths | later (end) of study |
|------------------------|---------------------------|------------------------------|----------------------|
|------------------------|---------------------------|------------------------------|----------------------|

Values are presented as mean \pm standard deviation.

After three months of wearing CGM, there was a slight increase in the average value of laboratory-measured glycated HbA1c compared to the initial measurement. These two parameters positively correlated, with a Pearson correlation coefficient of 0.542, p<0.05 (p=0.002). However, the paired samples t-test for this variable did not yield statistically significant results (t=-0.945, p=0.352). Further analysis divided participants into two groups based on initial HbA1c values: those with HbA1c equal to or less than 7%, and those with initial HbA1c greater than 7%. Among the participants with HbA1c \leq 7.00%, a statistically significant increase was observed. Their correlation was 0.847, p=0.0001, and the t-test value was t=-5.090, p=0.0002. In this group, HbA1c increased on average by 0.59±0.44%. Thus, the values from this group likely contributed to the overall increase in HbA1c in the sample. In the group with HbA1c > 7.0%, there was no statistically significant decrease, although the average HbA1c at the beginning was 7.78±0.76% and at the end was 7.53±0.68%. The correlation between these variables was not significant (0.274, p=0.305), nor was the t-test (t=1.184, p=0.255).

Among all laboratory-measured parameters, statistically significant increases were observed in total cholesterol and TSH. Cholesterol increased by 0.19 ± 0.42 (t=-2.551, p=0.016), and there was a statistically significant correlation between initial and final cholesterol measurements (p<0.001), with a Pearson correlation coefficient of 0.884. Although the average cholesterol remained within the normal range in the group (4.19\pm0.88), the significant increase suggests an influence of sensor-augmented pump therapy. There were no statistically significant changes in cholesterol fractions, but HDL increased by 0.01 on average, while LDL decreased by 0.07. These parameters also showed a statistically significant positive correlation between initial and final measurements (p<0.001), with

coefficients of 0.929 for HDL and 0.879 for LDL. Triglycerides remained within normal limits after three months, despite an average increase of 0.07 ± 0.24 .

The influence of sensor-augmented pump therapy on other laboratory-measured parameters in our group was noticeable in TSH, also. TSH measurements at the beginning and end of the study showed a correlation of 0.753, p<0.001, and there was a statistically significant average increase in TSH across the group by 0.50 ± 0.90 , t=-2.922, p=0.007. Although the average TSH remained within the euthyroid range at 2.69 ± 1.88 , it exceeded 2.50 on average, as it was 2.22 ± 0.88 at the beginning of the study, indicating a shift from normal lower to normal higher values.

Other parameters describing thyroid function did not show statistically significant changes. FT4 values did not exhibit significant correlation between initial and final measurements (Pearson coefficient 0.071, p=0.711; t=1.453, p=0.157). Thyroid peroxidase antibodies (TPO antibodies) were measured at the end of the study, with values above or equal to 60 considered elevated. Out of 30 participants, 21 or 70% had TPO antibodies below 60, and 9 had higher values. The average value in the group with elevated antibodies was 808.33 ± 595.27 , while in the group with lower antibodies, it was 32.29 ± 6.50 . In the group with TPO antibodies below 60, TSH increased by 0.44 ± 0.99 on average, t=-2.01, p=0.058, while in the other group, it increased by 0.58 ± 0.66 , t=-2.632, p=0.030.

Based on TSH values, the entire group was divided into three subgroups: normal lower values (below 2.5), normal higher values (2.5 to 4.0), and higher values (above 4.0). The correlation values between parameters, both at the beginning and end of the study, as well as tstatistics for each group, are presented in Table 2.

| | 0.00 <tsh<2.50 n=14</tsh<2.50 | | | 2.50 <tsh<4.00 n=12</tsh<4.00 | | | | TSH>4.00 | | | | |
|-------------------|--------------------------------------|--------|--------|--------------------------------------|-------------------------|----------|--------|----------|-------------------------|-------|--------|-------|
| Variable | Pearson coefficients | p | t | р | Pearson coefficients | <u>р</u> | t | р | Pearson coefficients | p | t | р |
| Total cholesterol | 0.868 | <0.001 | -1.194 | 0.074 | 0.904 | <0.001 | -1.278 | 0.228 | 0.816 | 0.184 | -0.927 | 0.422 |
| HDL | 0.964 | <0.001 | -0.763 | 0.459 | 0.950 | < 0.001 | -0.085 | 0.934 | 0.140 | 0.860 | 0.225 | 0.836 |
| LDL | 0.866 | <0.001 | 0.956 | 0.356 | 0.908 | < 0.001 | -0.148 | 0.885 | 0.457 | 0.543 | 0.688 | 0.541 |
| Tryglicerides | 0.896 | <0.001 | -1.681 | 0.117 | 0.712 | 0.021 | -0.613 | 0.555 | -0.044 | 0.956 | -1.00 | 0.391 |
| FT4 | 0.263 | 0.364 | 2.463 | 0.028 | -0.388 | 0.213 | -0.087 | 0.932 | 0.521 | 0.479 | -2.784 | 0.069 |
| HbA1c | 0.506 | 0.065 | 0.811 | 0.432 | 0.690 | 0.013 | -1.966 | 0.075 | 0.930 | 0.070 | -3.018 | 0.057 |
| BMI | 0.982 | <0.001 | -0.321 | 0.754 | 0.857 | <0.001 | -0.763 | 0.462 | -0.972 | 0.028 | 3.398 | 0.043 |

Table 2: The Pearson correlation coefficients between the measured parameter values at the beginning and at the end of the study, and the paired sample t-test for the same parameters, according to subgroups based on TSH measured at the end of the study.

From the table, it is evident that variables in the first two groups correlated between measurements before and after three months, while in the third group, only BMI correlated. The third group had the smallest sample size (only 4 participants), so the negative correlation of BMI measurements may be incidental. In the group with higher normal TSH values, there were no statistically significant changes in parameters between parameters measurements, although correlated significantly and with high coefficients. HbA1c came closest, with t=-1.966, p=0.075, but statistical significance was not achieved, probably due to the small sample size. In the group with lower normal TSH values, FT4 showed statistical significance, although it did not

correlate significantly with measurements. FT4 decreased by 1.77 in this group after three months, and this decrease was statistically significant.

We investigated whether there were gender differences in some of these laboratory-measured variables using binary logistic regression analysis (Chi-square=16.1997, p=0.006), and found statistical significance for total cholesterol and FT4. The Exp (B) for total cholesterol was 5.830 (p=0.01), and for FT4, it was 0.35 (p=0.043). This indicates a 5.8 times higher chance in our study group that increased cholesterol is associated with girls, and similarly, a 0.35 times higher chance that increased FT4 is associated with girls.

Table 3: displays the values of parameters obtained from continuous glucose monitoring and total daily insulin dose over three months for the entire group, as well as subgroups determined based on TSH values.

Table 3: The parameters obtained from the ambulatory glucose profile after three months on insulin pump therapy assisted by a sensor for the entire group, as well as subgroups determined based on TSH values.

| Variable | Entire group | 0.00 <tsh<2.50< th=""><th>2.50<tsh<4.00< th=""><th>TSH>4.00</th></tsh<4.00<></th></tsh<2.50<> | 2.50 <tsh<4.00< th=""><th>TSH>4.00</th></tsh<4.00<> | TSH>4.00 |
|--------------------------|--------------|--|--|------------------|
| TIR (3.9 – 10.0 mmol/L) | 69.66±8.96 | 68.86±8.67 | 69.39±8.35 | 73.25±13.20 |
| TBR_I (3.0 – 3.9 mmol/L) | 1.93±1.13 | 2.16±1.29 | 1.92±0.97 | 1.17 ± 0.84 |
| TBR_II (<3.0 mmol/L) | 0.52±0.60 | 0.55±0.65 | 0.61±0.62 | 0.17±0.33 |
| TAR_I (10.0-13.9 mmol/L) | 22.19±5.69 | 22.29±5.82 | 22.47±3.74 | 21.00±10.61 |
| TAR_II (>13.9 mmol/L) | 5.84±3.75 | 6.17±3.43 | 5.94±4.46 | 4.42±2.99 |
| CV (%) | 34.10±3.64 | 35.02±3.12 | 34.11±3.60 | 30.84 ± 4.52 |
| SG (mmol/L) | 8.56±0.68 | 7.00±0.31 | 7.00±0.24 | 6.97±0.41 |
| GMI (%) | 7.00±0.28 | 8.55±0.74 | 8.59±0.58 | 8.50±0.92 |
| TDD (IU) | 45.16±19.21 | 45.50±20.29 | 46.23±20.17 | 40.79±16.20 |

Values are presented as mean \pm standard deviation.

It can be observed that participants in the group with high TSH values achieved the best results, but this subgroup had the smallest number of participants, making their results subject to chance. However, looking at the entire group, we can conclude that an increase in TSH within normal limits corresponds to an increase in TIR, and that the goals defined by consensus were achieved within three months.

In further analysis, we investigated which parameters from continuous glucose monitoring had the most impact on the laboratory-measured values. The Pearson correlation coefficients between parameters from continuous glucose monitoring and laboratory-measured parameters at the end of the study are presented in Table 4.

| Variable | Total cholesterol | HDL | LDL | Tryglicerides | TSH | FT4 | ТРО | HbA1c | BMI |
|---------------------|----------------------|---------|---------|---------------|---------|---------|---------|----------|---------|
| TIR | -0.071 | 0.147 | -0.025 | -0.376 | 0.227 | -0.382 | -0.106 | -0.771 | 0.133 |
| (3.9 – 10.0 mol/L) | (0.708) | (0.439) | (0.894) | (0.041) | (0.227) | (0.037) | (0.578) | (<0.001) | (0.484) |
| TBR_I | 0.122 | 0.253 | 0.011 | -0.063 | -0.277 | 0.213 | -0.385 | -0.195 | 0.279 |
| (3.0 - 3.9 mmol/L) | (0.522) | (0.177) | (0.953) | (0.740) | (0.138) | (0.259) | (0.035) | (0.302) | (0.135) |
| TBR_II | -0.042 | 0.230 | -0.181 | -0.15 | -0.223 | 0.235 | -0.319 | -0.004 | 0.424 |
| (<3.0 mmol/L) | (0.827) | (0.222) | (0.340) | (0.935) | (0.236) | (0.212) | (0.086) | (0.982) | (0.020) |
| TAR_I | 0.040 | -0.184 | 0.043 | 0.275 | -0.172 | 0.284 | 0.161 | 0.822 | -0.202 |
| (10.0-13.9 mmol/L) | (0.836) | (0.330) | (0.823) | (0.141) | (0.363) | (0.129 | (0.396) | (<0.001) | (0.284) |
| TAR_II | 0.060 | -0.200 | 0.009 | 0.494 | -0.137 | 0.380 | 0.159 | 0.627 | -0.140 |
| (>13.9 mmol/L) | (0.752) | (0.289) | (0.963) | (0.006) | (0.471) | (0.038) | (0.402) | (<0.001) | (0.461) |
| CV(0()) | 0.154 | 0.087 | 0.045 | 0.119 | -0.303 | 0.208 | -0.119 | 0.113 | 0.121 |
| | (0.416) | (0.646) | (0.815) | (0.530) | (0.103) | (0.269) | (0.530) | (0.552) | (0.523) |
| SG (mmol/L) | 0.035 | -0.259 | 0.041 | 0.425 | -0.084 | 0.308 | 0.274 | 0.782 | -0.232 |
| | (0.854) | (0.168) | (0.831) | (0.019) | (0.658) | (0.098) | (0.143) | (<0.001) | (0.217) |
| GMI (%) | 0.013 | -0.283 | 0.028 | 0.424 | -0.111 | 0.268 | 0.277 | 0.810 | -0.218 |
| | (0.944) | (0.129) | (0.881) | (0.020) | (0.558) | (0.152) | (0.138) | (<0.001) | (0.248) |
| | -0.176 | 0.029 | -0.318 | 0.288 | -0.001 | 0.544 | -0.170 | 0.040 | 0.434 |
| 100 (10) | (0.353) | (0.878) | (0.087) | (0.122) | (0.995) | (0.002) | (0.368) | (0.835) | (0.016) |

Table 4: Pearson correlation coefficients of parameters from the ambulatory glucose profile and parameters measured in the laboratory with p-values shown in parentheses.

From the table, it can be concluded that parameters obtained from continuous glucose monitoring do not positively, statistically significant correlate with cholesterol or its fractions, but they do correlate with triglycerides. A 1% increase in TIR leads to a decrease in triglycerides by 0.376. The negative correlation of TIR with this variable suggests that better glycemic control, or higher TIR, leads to a decrease in triglycerides. Additionally, triglycerides show positive correlation with time spent in extreme hyperglycemia and average sensor glucose concentration.

TSH also does not correlate with parameters from continuous glucose monitoring. FT4 shows a negative correlation with TIR and a positive correlation with extreme hyperglycemia and total daily dose. Interestingly, TPO antibodies are negatively correlated with time spent in hypoglycemia (between 3.0 and 3.9 mmol/L), while extreme hypoglycemia below 3.0 mmol/L positively correlates with increased BMI. BMI also positively correlates with total daily insulin dose.

DISCUSSION

The principal findings of our investigation reveal that sensor-augmented insulin pump therapy exerts an influence on thyroid-stimulating hormone (TSH) and total cholesterol levels in children diagnosed with type 1 diabetes mellitus (T1DM) after a three-month period. Despite the parameters remaining within normal ranges, there was a marginal elevation noted in both TSH and total cholesterol. The elevation in glycated hemoglobin (HbA1c), particularly notable in the cohort of children with an initial HbA1c level below 7.00%. is conjectured to stem from a reduction in hypoglycemic episodes from the preceding period that were undetected by continuous glucose monitoring devices, as the novel therapy offered the option to suspend insulin before reaching low glucose values. $^{\left[18-20\right] }$

In our study group, total cholesterol exhibited an increase of 0.19, primarily attributed to high-density lipoprotein (HDL) cholesterol, while low-density lipoprotein (LDL) cholesterol showed a decrement. This observation suggests that the elevation in total cholesterol was accompanied by an increase in favorable lipoprotein fractions, despite the lack of statistical significance in the cholesterol fractions upon repeated measurements after three months, which may be attributed to the small sample size, a primary limitation of this study. Alterations in total cholesterol and its fractions did not display significance even within subgroups stratified based on TSH values, although a higher likelihood of elevated total cholesterol values among female participants was observed.^[21,22]

Statistically significant correlations were observed between triglycerides and parameters derived from continuous glucose monitoring, notably a negative correlation with time spent in normoglycemia (3.9-10 mmol/L), suggesting that an augmentation in Time in Range (TIR) precipitates triglyceride reduction, indicative of enhanced metabolic control.^[23] Conversely, a positive correlation was noted between triglycerides and time spent in hyperglycemia exceeding 13.9 mmol/L, indicating that extreme hyperglycemia contributes to triglyceride elevation, likely attributed to increased dietary intake, a predominant cause of hyperglycemia.^[24]

Concerning the therapeutic impact on thyroid function, our analysis indicates a statistically significant increase in TSH levels, albeit all participants maintained euthyroid status. The most substantial elevation in TSH was observed in participants harboring thyroperoxidase antibodies exceeding 60 (Hashimoto's thyroiditis). While statistically significant correlations were demonstrated in repeated laboratory measurements among participants with lower normal and higher normal TSH values, no significant correlation was observed in euthyroid participants with TSH values above 4.0, or high values, with the exception of a negative correlation with body mass index (BMI), potentially attributable to the modest sample size of the study cohort.^[25,26] TSH did not exhibit a significant correlation with parameters derived from continuous glucose monitoring.

Existing literature underscores that prolonged elevations in TSH levels, even within normal ranges, predispose individuals to central obesity, insulin resistance, hyperglycemia, and other factors associated with cardiometabolic risk.^[27] However, no dependence of TSH on fasting glucose has been conclusively established in prior investigations. Studies exploring the interplay between lipid status, thyroid hormones, and diabetes parameters in the pediatric population are scarce, particularly those scrutinizing the association of these factors with parameters from continuous glucose monitoring. A Chinese study reported a negative correlation between TSH and HbA1c levels.^[28] While our study did not demonstrate a direct dependence of HbA1c on TSH, an escalation in both TSH and HbA1c was observed after three months, with the subgroup displaying the highest TSH values also exhibiting the highest TIR. Notably, TIR displayed a negative correlation with HbA1c, suggesting a potential correlation with TSH with an expanded sample size. All elevations remained within normal limits.

An intriguing observation in our investigation was the negative correlation between free thyroxine (FT4) and TIR, and a positive correlation with time spent in hyperglycemia exceeding 13.9 mmol/L, as well as total daily insulin dose. Additionally, a positive correlation was noted between the total daily insulin dose and BMI. Furthermore, BMI exhibited a positive correlation with time spent in hypoglycemia below 3.0 mmol/L, possibly attributed to uncontrolled dietary intake during hypoglycemic episodes, particularly prevalent in the pediatric population, leading to recurrent hyperglycemia, increased triglycerides, and elevated BMI.^[24]

In summary, our findings underscore a relationship between parameters of lipid status, thyroid hormone levels, and parameters derived from continuous glucose monitoring in our study cohort. Notably, an increase in TIR was associated with elevated total cholesterol, albeit at the expense of HDL, coupled with a reduction in LDL, indicating that enhanced regulation of glucose homeostasis translates into improved lipid status regulation, ultimately mitigating cardiometabolic risk, particularly pertinent in the pediatric population.^[29] Therefore, clinicians should incorporate lipid status into parameters biannual monitoring alongside

continuous glucose monitoring parameters to timely detect fluctuations and implement appropriate dietary interventions aimed at reducing cardiovascular risk in this demographic.^[30]

The primary limitation of our study lies in the modest sample size, precluding statistical significance for certain parameters. Nonetheless, this study serves as a foundational framework for further exploration, representing one of the few endeavors seeking to elucidate the connection between parameters obtained from continuous glucose monitoring, or novel parameters indicative of good glucose homeostasis, thyroid hormone levels, and lipid status in children with type 1 diabetes.

CONCLUSION

Children with diabetes necessitate comprehensive monitoring of all parameters for optimal metabolic control, encompassing thyroid hormone levels and lipid status alongside parameters derived from continuous glucose monitoring. Our study has unveiled an association between novel parameters of metabolic control derived from continuous glucose monitoring, not only with laboratory-measured HbA1c levels but also with thyroid hormone levels and lipid status. Future research endeavors should strive to validate this association on a larger scale and potentially derive a mathematical correlation to substantiate it. For enhanced metabolic control among pediatric individuals with type 1 diabetes, routine lipid status parameter analyses every six months are imperative to detect temporal fluctuations and facilitate timely interventions through appropriate dietary adjustments aimed at curtailing cardiovascular risk in this population.

LITERATURE

- Chiang, J.L., Maahs, D.M., Garvey, K.C., Hood, K.K., Laffel, L.M., Weinzimer, S.A., et al. Type 1 diabetes in children and adolescents: a position statment by the American Diabetes Association. Diabetes Care, 2018; 41(9): 2026-44. DOI: 10.2337/dci18-0023
- Naghavi M., Liane Ong K., Aali A., Ababneh H.S et al. Global burden of 288 causes of death and life expectancy decomposition in 204 countries and territories and 811 subnational locations, 1990–2021: a systematic analysis for the Global Burden of Disease Study 2021. The Lancet, 2024. Available online 3 April 2024 DOI:https://doi.org/10.1016/S0140-6736(24)00367-2.
- Dayal, Devi; Gupta, Brij Mohan1; Gupta, Atul. Thyroid disorders in children and adolescents: Systematic mapping of global research over the past three decades. Thyroid Research and Practice, Jan– Apr, 2021; 18(1): 23-30. | DOI: 10.4103/trp.trp_5_21
- 4. Al-Qahtani MH, ElYahia SA, AlQahtani AS, AlQahtani AJ, Alamer AA, AlQahtani SM, Yousef AA, Albuali WH, Awary BH, Aldajani AA, et al.

Thyroid Disorders Spectrum in Pediatric Endocrine Clinic; Seven-Year Experience of a Teaching Hospital in Saudi Arabia. Children., 2023; 10(2): 390. https://doi.org/10.3390/children10020390

- Jennifer M. Barker, Jeesuk Yu, Liping Yu, Jian Wang, Dongmei Miao, Fei Bao, Edward Hoffenberg, Jerald C. Nelson, Peter A. Gottlieb, Marian Rewers, George S. Eisenbarth; Autoantibody "Subspecificity" in Type 1 Diabetes: Risk for organspecific autoimmunity clusters in distinct groups. Diabetes Care 1 April, 2005; 28(4): 850–855. https://doi.org/10.2337/diacare.28.4.850
- Biondi B, Kahaly GJ, Robertson RP. Thyroid Dysfunction and Diabetes Mellitus: Two Closely Associated Disorders. Endocr Rev., 2019 Jun 1; 40(3): 789-824. doi: 10.1210/er.2018-00163. PMID: 30649221; PMCID: PMC6507635.
- Orzan A, Novac C, Mihu M, Tirgoviste CI, Balgradean M. Type 1 Diabetes and Thyroid Autoimmunity in Children. Maedica (Bucur), 2016 Dec; 11(4): 308-312. PMID: 28828047; PMCID: PMC5543522.
- Frommer L, Kahaly GJ. Type 1 Diabetes and Autoimmune Thyroid Disease-The Genetic Link. Front Endocrinol (Lausanne), 2021 Mar 10; 12: 618213. doi: 10.3389/fendo.2021.618213. PMID: 33776915; PMCID: PMC7988207.
- Eom YS, Wilson JR, Bernet VJ. Links between Thyroid Disorders and Glucose Homeostasis. Diabetes Metab J., 2022 Mar; 46(2): 239-256. doi: 10.4093/dmj.2022.0013. Epub 2022 Mar 24. PMID: 35385635; PMCID: PMC8987680.
- Aguayo-Mazzucato C, Zavacki AM, Marinelarena A, Hollister-Lock J, El Khattabi I, Marsili A, Weir GC, Sharma A, Larsen PR, Bonner-Weir S. Thyroid hormone promotes postnatal rat pancreatic β-cell development and glucose-responsive insulin secretion through MAFA. Diabetes, 2013 May; 62(5): 1569-80. doi: 10.2337/db12-0849. Epub 2013 Jan 10. PMID: 23305647; PMCID: PMC3636623.
- Nishi M. Diabetes mellitus and thyroid diseases. Diabetol Int., 2018 Mar 9; 9(2): 108-112. doi: 10.1007/s13340-018-0352-4. PMID: 30603357; PMCID: PMC6224947.
- Zhang J, Xiao Y, Hu J, Liu S, Zhou Z, Xie L. Lipid metabolism in type 1 diabetes mellitus: Pathogenetic and therapeutic implications. Front Immunol, 2022 Oct 6; 13: 999108. doi: 10.3389/fimmu.2022.999108. PMID: 36275658; PMCID: PMC9583919.
- Roth GA, Mensah GA, Johnson CO, et al. Global burden of cardiovascular diseases and risk factors, 1990–2019. J Am Coll Cardiol, 2020; 76(25): 2982– 3021, doi:10.1016/j.jacc.2020.11.010.
- 14. Dovc K, Battelino T. Time in range centered diabetes care. Clin Pediatr Endocrinol, 2021; 30(1):
 1-10. doi: 10.1297/cpe.30.1. Epub 2021 Jan 5. PMID: 33446946; PMCID: PMC7783127.
- 15. Vigersky RA, McMahon C. The Relationship of Hemoglobin A1C to Time-in-Range in Patients with

Diabetes. Diabetes Technol Ther., 2019 Feb; 21(2): 81-85. doi: 10.1089/dia.2018.0310. Epub 2018 Dec 21. PMID: 30575414.

- Battelino T, Danne T, Bergenstal RM, Amiel SA, Beck R et al. Clinical Targets for Continuous Glucose Monitoring Data Interpretation: Recommendations From the International Consensus on Time in Range. Diabetes Care, 2019 Aug; 42(8): 1593-1603. doi: 10.2337/dci19-0028. Epub 2019 Jun 8. PMID: 31177185; PMCID: PMC6973648.
- 17. Danne T, Nimri R, Battelino T et al. International Consensus on Use of Continuous Glucose Monitoring. Diabetes Care, 2017; 40: 1631–1640. | https://doi.org/10.2337/dc17-1600
- Marie Moth Henriksen, Henrik Ullits Andersen, Birger Thorsteinsson, Ulrik Pedersen-Bjergaard, Hypoglycemic Exposure and Risk of Asymptomatic Hypoglycemia in Type 1 Diabetes Assessed by Continuous Glucose Monitoring, The Journal of Clinical Endocrinology & Metabolism, June, 2018; 103(6): 2329–2335. https://doi.org/10.1210/jc.2018-00142
- Martín-Timón I, Del Cañizo-Gómez FJ. Mechanisms of hypoglycemia unawareness and implications in diabetic patients. World J Diabetes., 2015 Jul 10; 6(7): 912-26. doi: 10.4239/wjd.v6.i7.912. PMID: 26185599; PMCID: PMC4499525.
- Karges B, Rosenbauer J, Kapellen T, Wagner VM, Schober E, Karges W, Holl RW. Hemoglobin A1c Levels and risk of severe hypoglycemia in children and young adults with type 1 diabetes from Germany and Austria: a trend analysis in a cohort of 37,539 patients between 1995 and 2012. PLoS Med., 2014 Oct 7; 11(10): e1001742. doi: 10.1371/journal.pmed.1001742.
- Holven KB, Roeters van Lennep J. Sex differences in lipids: A life course approach. Atherosclerosis, 2023 Nov; 384: 117270. doi: 10.1016/j.atherosclerosis.2023.117270.
- 22. Robinson GA, Pineda-Torra I, Ciurtin C, Jury EC. Sex Differences in Lipid Metabolism: Implications for Systemic Lupus Erythematosus and Front Cardiovascular Disease Risk. Med (Lausanne), 2022 May 31; 9: 914016. doi: 10.3389/fmed.2022.914016.
- 23. Kosmas CE, Silverio D, Sourlas A, Garcia F, Montan PD, Guzman E. Impact of lipid-lowering therapy on glycemic control and the risk for newonset diabetes mellitus. Drugs Context, 2018 Nov 28; 7: 212562. doi: 10.7573/dic.212562.
- 24. Mottalib A, Kasetty M, Mar JY, Elseaidy T, Ashrafzadeh S, Hamdy O. Weight Management in Patients with Type 1 Diabetes and Obesity. Curr Diab Rep., 2017 Aug 23; 17(10): 92. doi: 10.1007/s11892-017-0918-8.
- 25. Solanki A, Bansal S, Jindal S, Saxena V, Shukla US. Relationship of serum thyroid stimulating hormone with body mass index in healthy adults. Indian J

Endocrinol Metab., 2013 Oct; 17(Suppl 1): S167-9. doi: 10.4103/2230-8210.119560

- Velluzzi F, Pisanu S, Galletta M, Fosci M, Secci G, Deledda A, Boi F, Rodia R, Fanciulli G, Delitala AP, Sainas G, Loviselli A. Association between High Normal TSH Levels and Obesity in Women with Anti-Thyroid Autoantibodies (ATAs). J Clin Med., 2022 Aug 31; 11(17): 5125. doi: 10.3390/jcm11175125.
- 27. Chang YC, Hua SC, Chang CH, Kao WY, Lee HL, Chuang LM, Huang YT, Lai MS. High TSH Level within Normal Range Is Associated with Obesity, Dyslipidemia, Hypertension, Inflammation, Hypercoagulability, and the Metabolic Syndrome: A Novel Cardiometabolic Marker. J Clin Med., 2019 Jun 7; 8(6): 817. doi: 10.3390/jcm8060817.
- 28. He J, Lai Y, Yang J, Yao Y, Li Y, Teng W, Shan Z. The Relationship Between Thyroid Function and Metabolic Syndrome and Its Components: A Cross-Sectional Study in a Chinese Population. Front Endocrinol (Lausanne), 2021 Mar 31; 12: 661160. doi: 10.3389/fendo.2021.661160.
- Starnberg J, Norman M, Westrup B, Domellöf M, Berglund SK. Cardiometabolic risk factors in children born with marginally low birth weight: A longitudinal cohort study up to 7 years-of-age. PLoS One, 2019 Apr 19; 14(4): e0215866. doi: 10.1371/journal.pone.0215866
- Yuan C, Sun X, Liu Y, Wu J. The thyroid hormone levels and glucose and lipid metabolism in children with type 1 diabetes: a correlation analysis. Transl Pediatr, 2021 Feb; 10(2): 276-282. doi: 10.21037/tp-20-204.