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Correlation between Glycated Hemoglobin and Calcium Levels in Pediatric with Type 1 Diabetes Mellitus

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ABSTRACT

Introduction: Type 1 diabetes mellitus is a systemic disorder resulting from impaired glucose metabolism characterized by chronic hyperglycemia. Caused by damage to pancreatic β cells either by autoimmune or idiopathic processes resulting in reduced or even halted insulin production. Diabetes mellitus is associated with a decrease in calcium with impaired intestinal calcium absorption and hypercalciuria which causes a decrease in calcium absorption into the body.

Method: This study used a prospective study method to assess the correlation between HbA1C levels and calcium levels in children with type 1 diabetes mellitus. This research was conducted in the Endocrinology Outpatient Unit of Haji Adam Malik Hospital Medan, May 2022 to December 2022. The samples were children aged 1 month to 18 years.

Results: Correlation is measured using Pearson correlation analysis for normally distributed data while Spearman correlation is used for data that was not normally distributed. There is a significant correlation between the HbA1c and calcium levels with a p value of 0.026 and a correlation value of (r= -0.445). The correlation value is negative, meaning that every increase in HbA1c levels will be followed by a decrease in serum calcium levels in children with type I diabetes, with moderate strength (r= 0.4 – 0.6). This effect is not influenced by diseases duration and onset of diabetes.

Conclusion: There is a decrease in calcium in type 1 diabetes.

Keywords

Diabetes mellitus type 1, HbA1c, Calcium, Pediatric

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INTRODUCTION

Type 1 diabetes mellitus is caused by damage to pancreatic β-cells either by autoimmune or idiopathic processes resulting decresead or halted insulin production. Around 96,000 children under 15 years old worldwide are estimated to suffer from type 1 diabetes every year. In most western countries, type 1 diabetes accounts for more than 90% of diabetes in childhood and adolescence. However, the incidence of type 1 and type 2 diabetes may differ across populations with different age and racial/ethnic distributions. For example, the highest prevalence of type 1 diabetes in the United States is found among white adolescents and the lowest among American Indian adolescents, with prevalence rates of 2.55 per 1000 and 0.35 per 1000.[1,2]

The Diabetes Control and Complication Trial (DCCT) states that proper glucose control will produces good glycemic targets and prevents complications. Short-term complications that often occur are hypoglycemia and DKA. Long-term complications include kidney disorders, retinopathy, neuropathy, cardiovascular disease. Another complication that can occur is osteopenia which occurs due to increased osteoclast activity which causes increased bone resorption. Insulin deficiency will cause a decrease in bone mass synthesis and glucosuria which causes hypercalciuria.[2]

Type 1 diabetes mellitus is associated with a decrease in calcium level and impaired intestinal calcium absorption, which causes a decrease in calcium absorption into the body. Type 1 diabetes mellitus is associated with low bone mineral density and osteoporosis. Calcium itself is an important element for several biological processes, such as bone formation. Several studies have proven that low calcium level in diabetes patients is associated with osteoporosis and increased risk of bone fractures.[3]

Hemoglobin A1c (glycated hemoglobin, glycosylated hemoglobin, HbA1c, or A1c) is used to evaluate individual's glucose control. The test shows the average blood sugar level for the last 90 days. HbA1c measurement can be used the risk of long-term complications and as a tool to optimize glycemic control.[4,5]

Calcium homeostasis refers to the hormonal regulation of ionized calcium by parathyroid hormone, 1,25-dihydroxyvitamin D, and ionized serum calcium itself, which together regulate calcium transport in the intestines, kidneys, and bones.9 In diabetes, there is a disturbance in calcium metabolism, resulting in a decrease in calcium which is related to bone quality. Diabetes mellitus also causes bone mineral density disorders which can lead to osteoporosis or bone fractures.[3,7]

Diabetes mellitus is associated with calcium wasting in the kidneys, some reports that hyperglycemia causes hypercalciuria. Upregulation of the expression of transcellular calcium transporting proteins (e.g., TRPV5 and calbindin-D 28k), but not of paracellular proteins (i.e., claudin-16, normally required for calcium and magnesium reabsorption in the ascending limb of the loop of Henle) in the renal tubules of diabetic STZ-induced rats, suggesting that this is a compensatory response to long-term renal calcium wasting.[8]

METHOD

This research was a prospective study to assess the correlation between HbA1c l and calcium levels in children with Type 1 diabetes in the Pediatric Endocrinology Outpatient Unit of Haji Adam Malik hospital, Medan, North Sumatra, Indonesia over a period of eight months, from May 2022 to December 2022.

Subjects who participated in the study children aged 1 month to 18 years who came to the endocrine clinic with type 1 diabetes without comorbidities such as chronic kidney disease and thyroid disease.

Univariate and bivariate analyses were carried out using a statistical computer software (SPSS). Univariate analysis was conducted to describe the research subjects. Categorical data was presented in frequency and percentage. Numerical data was presented in mean ± standard deviation for normal distribution data, otherwise median (range) for non-normal distribution data. The analyzes were carried out using unpaired t-rest (for normal distribution) or Mann-Whitney test (for non-normal distribution). Spahiro-Wilk test was used for the test of normality. The significance level and confidence interval used were $p<0.05$ and 95% (CI 95%).

RESULT

This study involved 24 children atients with Type 1 diabetes in the Pediatric Endocrinology Outpatient of Haji Adam Malik hospital, Medan, North Sumatra, Indonesia. There were 5 (20,8%) male patients and 19 (79,2%) female patients. More than half (19 patients, 79.16%) were 12 – 18 years. One patient was under 5 years (4,18%) and 4 remaining patients (16,6) were 6 – 12 years. Nutritional status of the subjects were malnutrition in 11 patients (45,8%), and good nutritional status in 13 patients (54,2%) which was summarized in the Table 1.

The mean HbA1c level was 12.94% (SD = 2.71%) with the lowest level being 6.9% and the highest being 17.9%. Meanwhile, the mean calcium level was 8.48 mg/dL (SD = 0.74 mg/dL) with the lowest level being 7.4 mg/dL and the highest being 10.8 mg/dL which can be seen in Table 2.

Using the Spearman Correlation test, a significant correlation was found between the HbA1 c value ($p=0.026$) and calcium levels with a correlation value of -0.445. The correlation value is negative, meaning that every increase in HbA1c levels will be followed by a decrease in serum calcium levels in children with type I diabetes, with moderate strength (r value > 0.4 – 0.6) which can be seen in figure 1.

No significant correlation was found between the diseaseduration of diabetes and HbA1c levels in children suffering from type 1 diabtes ($p=0.074$).

Meanwhile, using the Spearman correlation test there was a significant correlation between age of onset and HbA1c levels (p=0.025). The correlation value obtained was -0.456. The negative sign indicates that as the age of onset increases, the HbA1c level will decrease. The strength of the correlation obtained was moderate correlation (p>0.4-0.6). which can be seen in Table. 3 and figure 2.

Using the Spearman Correlation test, no significant correlation was found between calcium levels and duration of suffering from type 1 diabetes and age of onset (p= 0.175) and (p= 0.72).which can be seen in the Table 4.

Table 1. Demographic Characteristic of Type 1 Diabetes

Subject Characteristics	n = 24
Gender, n (%)	
Male	5 (20,8)
Female	19 (79,2)
Age, months,	
1 year – 5 years	1 (4,18)
6 years – 12 years	4 (16,66)
12 years – 18 years	19 (79,16)
Body Weight, Kg (%)	
Mean (SD)	37,04 (11,25)
Median (Min – Max)	37,95 (12 – 52)
Height, cm	
Mean (SD)	142,75 (13,68)
Median (Min – Max)	146,5 (98 – 156)
Nutritional Status	
Malnutrition	11 (45,8)
Good Nutrition	13 (54,2)
Age og Onset of diabetes, years	
Mean (SD)	8,88 (2,83)
Median (Min – Max)	9,5 (5 – 15)
Duration of Diabetes (Years)	
Mean (SD)	3,83 (2,39)
Median (Min – Max)	3 (1 – 10)
Family History	
Mother	6 (25)
Grandpa	1 (4,2)
Grandma	3 (12,5)
Uncle	1 (4,2)
None	13 (54,1)

Table 2 HbA1c and Calcium in Children Type 1 Diabtes

Variable	n = 24
HbA1c %	
Mean (SD)	12,94 (2,71)
Median (Min-Max)	13,45 (6,9 – 17,9)
Calcium mg/dL	
Mean (SD)	8,48 (0,74)
Median (Min-Max)	8,3 (7,4 – 10,8)

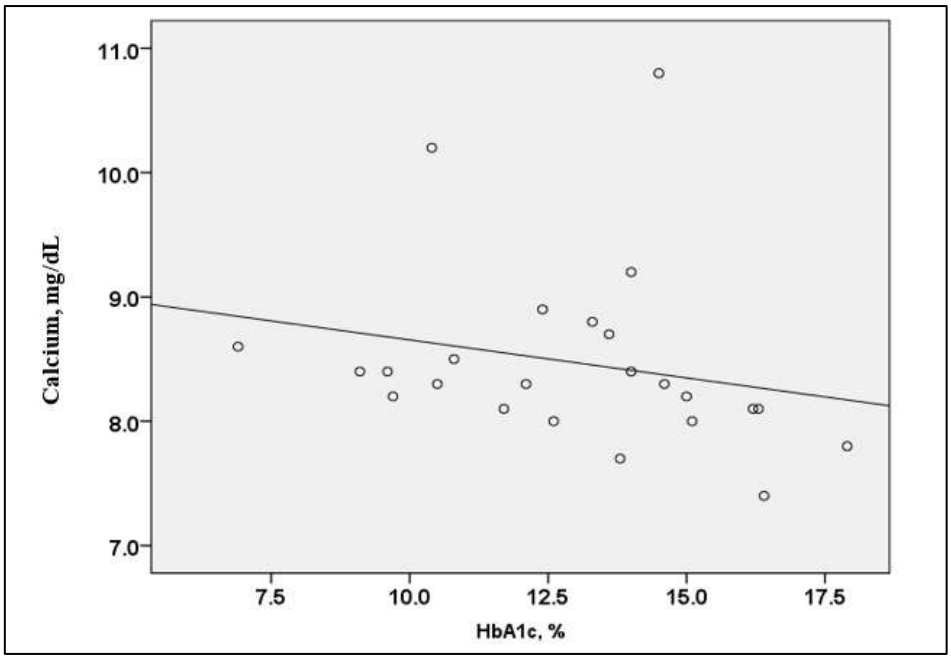

Figure 1. Scatter plot graphs of HbA1c with calcium levels with children type 1 diabetes

Table 3. Correlation between HbA1c between Calcium Levels, Duration of diabetes, Age

	HbA1c	
	p	r
Calcium	0.026	-0,445
Duration of diabetes	0,074	-0,371
Age of onset	0,025	-0,456

Table 3 Calcium levels, duaration of diabetes, and age of onset in children type 1 diabetes

	Calcium, mg/dL	
	p	r
Duration of diabetes	0,175	0,286
Age ogf onset	0,72	0,374

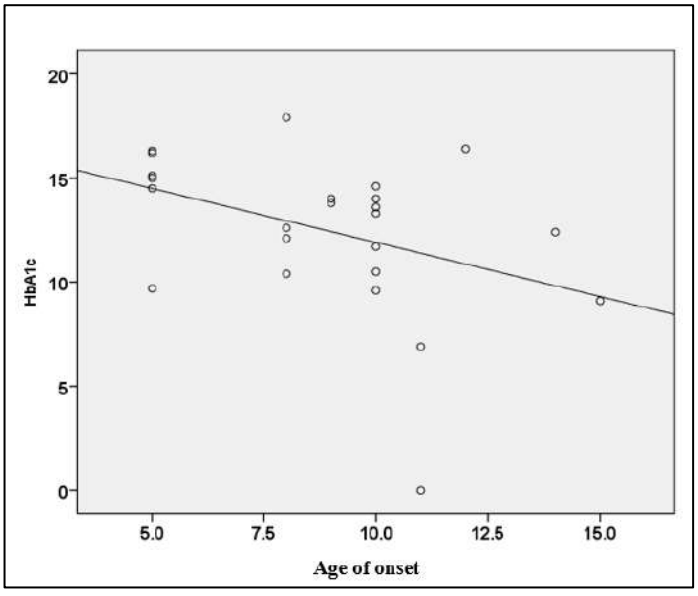

Figure 2. Scatter plot graphs of HbA1c with age of onset with children type 1 diabetes

DISCUSSION

According to the Indonesian Pediatrician Association (IDAI), in 2018, women were more likely to suffer from Type 1 diabetes (60%) than men (28.6%).[9] However, Harvey et al said that examined 4151 children with Type 1 diabetes in Wales, United Kingdom. male dominant as much as 51.7%. The incidence varies greatly with gender at different ages. Type 1 diabetes before the age of 2 years and after the age of 12 years is more common in boys. Testosterone levels in male babies peak at 6 - 12 weeks of age and decrease slowly from 3 months of age. At the age of nine to ten years, when girls reach puberty, type 1 diabetes occurs more often in girls. Thus analysis of the number of participants according to individual age at diagnosis showed that the influence of sex hormones was clearly visible in both pubertal males and females. Sex hormone effects have also been implicated in the peak incidence previously seen in older boys compared to girls.[5]

Sex differences in the incidence of type 1 diabetes are found in some but not all populations. However, persistent male gender bias in various countries is generally observed in older adolescents and young adults.[1] This study found that of 24 patients, 79.2% of patients were female, the male patients were only 20.8%.

The largest age group is the youth group aged 12 - 20 years, totaling 19 people, with the youngest being the preschool group, aged 1 - 5 years, 1 person. Throughout the world, it is estimated that 79, 100 children aged <15 years suffer from type 1 diabetes every year. In 2008 – 2009 for the US adolescent population, data from the SEARCH for Diabetes in Youth study estimated that in adolescents aged <20 years, approximately 18,000 new cases of type 1 diabetes occurred per year. In the 0-19 year age group, type 1 diabetes accounts for 79% of all new cases of diabetes, 93% for non - Hispanic whites, 67% for Hispanics, 58% for Asians or Pacific Islanders, 52% for non-Hispanic blacks and 24% for American Indians or Alaska Natives.[10] The average age of first diagnosis or new onset of type 1 diabetes in this study was 8.88 years, with the youngest age being 5 years and the oldest age being 15 years. Research conducted in China by Peng et al over 10 years saw a progressive increase in the number of patients aged < 16 years diagnosed with type 1 diabetes, increasing from around 39 cases per year in 2009 – 2010 to 95 cases per year in 2017 – 2018. Results In Peng's research, 681 children and adolescents were diagnosed as < 2 years old, 59 children, 122 children aged 2 - 4 years, 281 children aged 5 - 9 years, and > 10 years old, 219 children.[11]

In this study, type 1 diabtes disease duration was also recorded with an average of 3.83 years with a duration range of 1 year to 10 years. Nutritional status according to CDC 2000 criteria weight for height (% median) Obesity >120, overweight >110, normal >90, malnutrition 70 – 90, malnutrition <70. In this study, based on nutritional status, there were 13 children with good nutrition and 11 children with poor nutrition.[12]

In pediatric patients with type 1 diabetes, 0 - 13% were reported to have first degree relatives and 32 - 52% of other family members were affected by type 2 diabetes.[13] In this study there were 13 people who had no family history of suffering from diabetes and the remaining 11 people had family who had diabetes. Suffering from diabetes and the mother suffering from diabetes was the highest family history suffering from diabetes in this research, around 6 people.

The correlation between serum calcium levels and HbA1c levels in type 2 diabetes has been studied in Sudan by Hassan et al. This is similar to the current research but differs in the study participants, namely the type of diabetes and age, the research we conducted was type 1 diabetes and in children. A statistically significant negative correlation was found in Hassan et al's study between HbA1c levels and serum calcium levels (r = - 0.56, p.value = 0.00) finding that hyperglycemia causes excess urinary calcium and phosphorus excretion in patients with Non-Insulin Dependent Diabetes Mellitus (NIDDM).[14]

In this research, the correlation results were negative, which means that every increase in HbA1c levels with a decrease in serum calcium levels in children suffering from type 1 diabetes with moderate strength (r value > 0.4 – 0.6), the possible cause of the decrease in calcium levels in type 1 diabetes is also due to by hyperglycemia which causes hypercalciuria. This is in line with research by Weber et al examining 20 teenage girls suffering from type 1 diabetes. Five participants were found to have estimated calcium retention values. Participants with negative calcium retention had greater median urinary calcium excretion compared with those with positive calcium retention. Diabetes-related outcomes (HbA1c, insulin dose, disease duration) and

urinary n-telopeptides (NTX) did not differ between those with positive versus negative calcium retention. Two participants (10%) were found to have hypercalciuria defined by 24-hour urinary calcium above 4 mg/kg/day. There was a significant correlation between 24 hour urine calcium and HbA1c.[15]

The results of research by Hasyim et al., total calcium showed a negative correlation with HbA1c and also in this study the albumin to creatinine ratio (ACR) showed an increase in patients with new onset diabetes, then decreased to almost normal with long duration of diabetes. This can be associated with and exacerbated by chronic uncontrolled hyperglycemia.[16] In this study, there was a correlation between the duration of suffering from diabetes and HbA1c levels in children suffering from type 1 diabetes ($p = 0.074$). This study also agrees with Luczynski that there is no correlation between disease duration and glycemic control.[17]

Meanwhile, using the Spearman correlation test, there was a significant correlation between age of onset and HbA1c levels ($p=0.025$), indicating that as the age of onset increases, the HbA1c levels will decrease. Current international guidelines recommend that children <18 years maintain HbA1c <53 mmol/mol (<7.0%) or as low as possible to reduce the risk of long-term diabetes. In this research there are several limitations, this research should carry out a calcium food recall so that the results will be even better. The urine calcium examination required at the hospital requires 24 h urine, so it is quite difficult for patients to do it.

CONCLUSION

There is a decrease in calcium levels in type 1 diabetes patients. There is a significant correlation between Hba1c values and calcium levels. There is a negative correlation between Hba1c levels and calcium levels, meaning that every increase in Hba1c levels will be followed by a decrease in calcium levels. There is poor metabolic control in research participants with average Hba1c levels > 7.5%

DECLARATIONS

Ethics approval and consent to participate. Permission for this study was obtained from the Ethics Committee of Universitas Sumatera Utara and Haji Adam Malik General Hospital.

CONSENT FOR PUBLICATION

The Authors agree to publication in Journal of Society Medicine.

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COMPETING INTERESTS

The authors declare that there is no conflict of interest.

AUTHORS' CONTRIBUTIONS

All authors significantly contribute to the work reported, whether in the conception, study design, execution, acquisition of data, analysis, and interpretation, or in all these areas. Contribute to drafting, revising, or critically reviewing the article. Approved the final version to be published, agreed on the journal to be submitted, and agreed to be accountable for all aspects of the work.

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