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Evaluation of the Hemoglobin A1c Test in Detecting Pediatric Prediabetes

Pediatrik Prediyabetin Tespitinde Hemoglobin A1c Testinin Değerlendirilmesi

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Abstract

Aim: It was aimed to evaluate the diagnostic performance of the hemoglobin A1c (HbA1c) test in pediatric prediabetes, and to determine the cut-off value for the adolescent.

Material and Method: This study was carried out by retrospectively evaluating the data of 379 adolescents aged between 10 and 18 years. Prediabetes was diagnosed based on glucose criteria, either the fasting glucose value or the 2-hour (2h) glucose value during a 75 g oral glucose tolerance test (OGTT), or HbA1c criteria. The sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were calculated for fasting, OGTT 2h glucose, and HbA1c. The area under the curve (AUC) was calculated for each test by receiver-operating characteristic analysis.

Results: 2.1% of individuals were assigned to the diabetes mellitus group, 21.9% to the prediabetes group, and 76.0% to the normoglycemia group. When 5.7 was used as the threshold value for HbA1c in prediabetes, the sensitivity was 53.0%. The AUC was 0.83 for the HbA1c test. An HbA1c threshold of 5.55% was determined as the optimal cut-off for diagnosing prediabetes, with 62.7% sensitivity and 93.0% specificity.

Conclusion: Although the use of adults' HbA1c criteria for the diagnosis of prediabetes in the pediatric ages is controversial due to the differences between the results of glucose and HbA1c-based tests, prediabetes screening is still important. HbA1c≥5.55 will be useful to follow up on adolescents with prediabetes in terms of risk and to screen them with blood glucose.

Keywords: HbA1c, pediatric prediabetes, diagnostic performance

Öz

Amaç: Hemoglobin A1c (HbA1c) testinin pediatrik prediyabet açısından tanısal performansının değerlendirilmesi, adolesan yaş grubu için cut-off değer belirlenmesi amaçlandı.

Gereç ve Yöntem: Çalışma, yaşları 10-18 yıl arasında değişen toplam 379 çocuğa ait verinin retrospektif değerlendirilmesiyle gerçekleştirildi. Prediyabet vakaları glukoz [açlık ve 75 g oral glukoz tolerans testi (OGTT) 2. Saat (2. sa)] ve Hba1c kriterlerine göre belirlendi. Sensitivite, spesifite, pozitif prediktif değer (PPV), negatif prediktif değer (NPV) ve ROC (receiver-operating characteristic) analiziyle AUC (area under the curve); açlık ve OGTT 2 sa glukozu, HbA1c testlerinin her biri için hesaplandı.

Bulgular: Bireylerin %2.1'i diabetes mellitus, %21.9'u prediyabet, %76.0'ı ise normoglisemi grubuna atandı. Prediyabette HbA1c testi için 5.7 değeri cut-off olarak alındığında sensitivite %53.0 olarak hesaplandı. HbA1c testi için AUC 0.83 olarak hesaplandı. HbA1c opimal cut-off değeri %5.55 olarak belirlendi. Bu değerde sensitivite %62.7, spesifite ise %93.0 olarak hesaplandı.

Sonuç: Pediatrik yaşlarda prediyabet tanısında erişkin HbA1c kriterlerinin kullanımı glukoz ve HbA1c temelli test sonuçları arasındaki farklılıklar nedeniyle tartışmalı olsa da prediyabet taraması önemini korumaktadır. HbA1c ≥ 5.55 değerinin prediyabetli adolesanların risk açısından takip edilmesi ve kan glukoz düzeyiyle taranması konusunda faydalı olacağı kanaatindeyiz.

Anahtar Kelimeler: HbA1c, pediatrik prediyabet, tanısal performans

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INTRODUCTION

Diabetes mellitus (DM), a disorder characterized by hyperglycemia resulting from impaired insulin secretion and/or insulin activity, is one of the most common chronic diseases in children.[1] Conditions in which plasma glucose and hemoglobin A1c (HbA1c) levels are higher than normal but do not reach the diagnostic limits of diabetes are called prediabetes.

Fasting plasma glucose and oral glucose tolerance test (OGTT) 2-hour (2h) plasma glucose are accepted as the conventional tests in the diagnosis of DM. However, these tests require fasting and preliminary preparation. The HbA1c test, on the other hand, is a simpler and more applicable test that does not require fasting. It can also be used as an indicator of chronic hyperglycemia.[2]

HbA1c is a subfraction of glycohemoglobin that is formed non-enzymatically due to glucose exposure. It is continuously produced in vivo by glucose forming a ketoamine at the beta chain N-terminus of hemoglobin. For this reason, HbA1c is used to monitor glucose levels because it is correlated with extracellular glucose levels and provides an estimate of average glucose levels for the last 120 days.[3]

An HbA1c of 5.7-6.4%, provided it was obtained by a standardized analysis, indicates prediabetes.[4] In addition to the differences in its standardization of HbA1c, the use of the same values in the pediatric age groups is highly controversial, since the cut-off values of the HbA1c test are mostly used in adults.[5,6] This study aimed to evaluate the diagnostic performance of the HbA1c test in prediabetes and to determine the cut-off value for adolescents.

MATERIAL AND METHOD

This study was carried out by retrospectively evaluating the data of 379 children aged between 10 and 18 years who applied to Yüzüncü Yıl University Dursun Odabaş Medical Center and underwent OGTT. Individuals with Hb<11 mg/dL and/or who were determined to have any hemoglobinopathy were not included in the study. Fasting glucose levels were measured in blood taken after at least 8-10 hours of fasting. Two-hour data after a 1.75 g/kg (maximum 75 g) oral glucose load were used to evaluate OGTT 2h glucose levels. Normoglycemia was determined at a fasting serum glucose of less than 100 mg/dL and an OGTT 2h serum glucose of less than 140 mg/dL and an HbA1c of less than 5.7%. Prediabetes was diagnosed based on glucose criteria, either the fasting glucose value or the 2h glucose value during a 75g OGTT, or HbA1c criteria. An HbA1C of 5.7-6.4% and/or fasting serum glucose of 100-125 mg/dL and/or an OGTT 2h serum glucose of 140-199 mg/dL resulted indicating prediabetes. Diabetes was diagnosed when the fasting serum glucose level was greater than or equal to 126 mg/dL, the OGTT 2h serum glucose level was greater than or equal to 200 mg/dL, and the HbA1c level was greater than or equal to 6.5%.[4] Serum glucose levels were analyzed by the hexokinase method, and HbA1c levels were analyzed by the high-performance liquid chromatography (HPLC) method.

The sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were calculated for HbA1c, fasting, and OGTT 2h glucose tests. The area under the curve (AUC) was calculated for each test by receiver-operating characteristic (ROC) analysis. The Youden index was used to determine the optimal cut-off values ["J=maximum (sensitivity+specificity −1)"].[7] The Mann-Whitney U test was used to evaluate the difference in HbA1c and glucose levels according to gender. A Spearman correlation analysis was performed to determine the correlation between HbA1c and blood glucose values. Analyses were performed using Microsoft Excel v2019 and IBM SPSS Statistics 22 programs. p-value < 0.05 was considered statistically significant.

RESULTS

59.6% (226) were female, and 40.4% (153) were male. The mean age was 14.0±2.5 years. Eight (2.1%) of 379 individuals were assigned to the DM, 83 (21.9%) to prediabetes, and 288 (76.0%) to normoglycemia groups. Since the number of patients with DM was small, they (n=8) were not included in the statistical analysis. The median (min-max) values of tests are summarized in **Table 1**. When grouped according to gender, fasting glucose levels were found to be higher in males compared to females (p=0.002). There was no difference between OGTT 2h glucose and HbA1c levels in terms of gender (p=0.096, 0.385).

The sensitivity, specificity, PPV, and NPV for HbA1c, fasting, and OGTT 2h glucose tests are shown in **Table 2**. When 5.7 was used as the threshold value of HbA1c in prediabetes, the sensitivity was 53.0%. An HbA1c threshold of 5.55% was determined as the optimal cut-off for diagnosing prediabetes, with 62.7% sensitivity and 93.0% specificity. Since each of the three tests was used as the gold standard, specificity and PPV were 100% as expected (**Table 2**). The AUC values analyzed by the ROC curve were 0.86, 0.72, and 0.83 for fasting glucose, OGTT 2h glucose, and HbA1c tests, respectively (**Figure 1**).

Table 1. Data for groups and tests.

	Number (%)	Fasting serum glucose (mg/dL)	OGTT 2h serum glucose (mg/dL)	HbA1c (%)
All	379 (100)	92.0 (62.0-158.0)	103.0 (50.0-245.0)	5.3 (4-8.7)
Normoglycemia	288 (76.0)	90.0 (62.0-99.0)	99.0 (50.0-136.0)	5.3 (4.0-5.6)
Prediabetes	83 (21.9)	102.0 (76.0-125.0)	114.0 (75.0-187.0)	5.7 (4.7-6.4)
Diabetes Mellitus	8 (2.1)	132.0 (100.0-158.0)	187.5 (113.0-245.0)	6.1 (5.1-8.7)

The test results for each group were expressed as a median (min-max).

Table 2: Diagnostic performance values of tests for diagnosing prediabetes.

	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	AUC
HbA1c (≥%5,7)	53.0	100	100	88,1	0,83
Fasting glucose (≥100 mg/dL)	60.2	100	100	89.7	0,86
OGTT 2h glucose (≥140 mg/dL)	18.1	100	100	80.9	0,72

OGTT: Oral glucose tolerance test, PPV: Positive predictive value, NPV: Negative predictive value, AUC: Area under the curve.

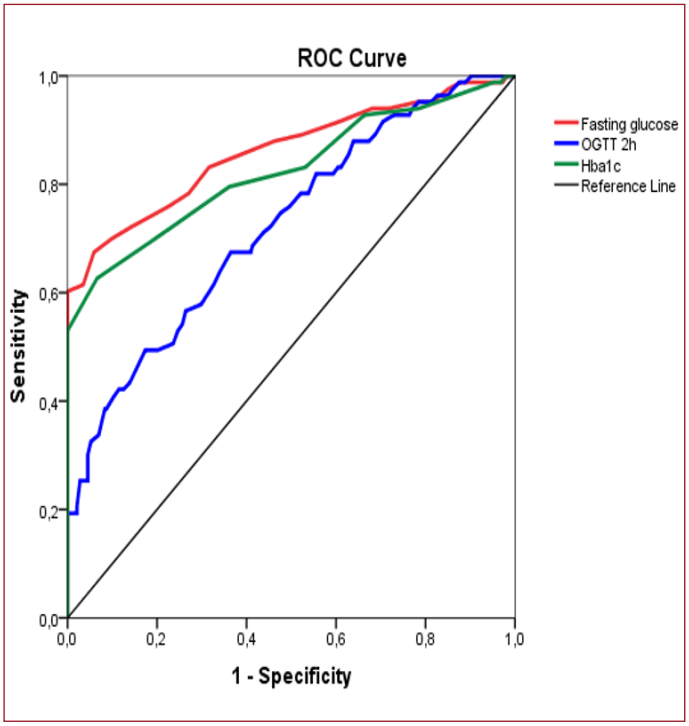

Figure 1. Receiver operating characteristic (ROC) curves comparing serum fasting glucose (red), oral glucose tolerance test (OGTT) 2 hour (2h) glucose (blue), and HbA1c (green) for the detection of prediabetes. The AUC (area under the curve) of the tests was calculated as 0.86, 0.72, and 0.83 for fasting glucose, OGTT 2h glucose, and HbA1c, respectively.

According to the HbA1c test, 25 prediabetic cases and one diabetic case did not meet the blood glucose criteria. According to the fasting glucose, 29 prediabetic and three diabetic cases did not meet both OGTT 2h glucose and Hba1c criteria. According to the OGTT 2h glucose, six prediabetic cases, and one diabetic case did not meet both fasting glucose and Hba1c criteria (**Figure 2, 3**). It was determined that HbA1c values were moderately correlated with fasting glucose values (r=0.306; p <0.001), while HbA1c levels were correlated with OGTT 2h glucose at a low degree (r=0.213; p <0.001). Fasting glucose values were moderately correlated with OGTT 2h glucose values (r=0.329; p <0.001).

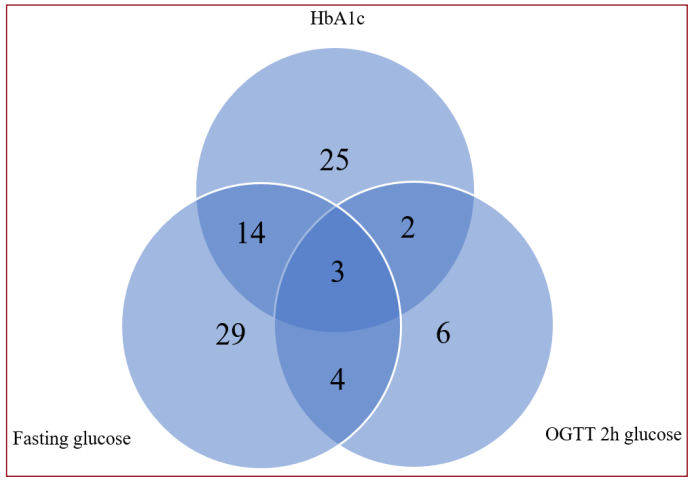

Figure 2. Venn Diagrams for Prediabetes. Prediabetes diagnosed by HbA1c 5.7-6.4% (n=44) or fasting glucose 100-125 mg/dL (n=50) or OGTT 2h glucose 140 mg/dL-199 mg/dL (n=15).

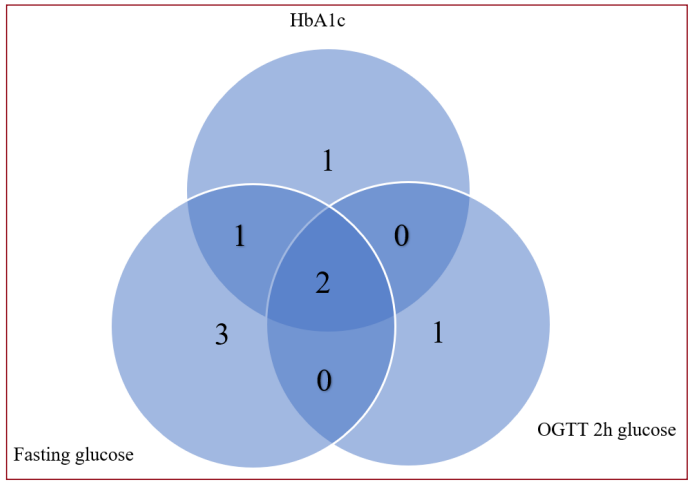

Figure 3. Venn Diagrams for Diabetes mellitus. Diabetes diagnosed by HbA1c ≥ 6.5% (n=4) or fasting glucose ≥ 126 mg/dL (n=6) or OGTT 2h glucose ≥ 200 mg/dL (n=3)

DISCUSSION

In this retrospective study, 21.9% (n=83) of the individuals who underwent OGTT had prediabetes. In the study, it was observed that the HbA1c ≥5.7 criteria had low sensitivity in the diagnosis of prediabetes for adolescents from the Van region of Turkey. We recommend an HbA1c value of 5.55% as an optimal cut-off to screen for prediabetes. This is a unique study evaluating the performance of HbA1c in the diagnosis of prediabetes and its relationship with serum glucose levels in adolescents in the Van region.

The prevalence of DM is increasing in both children and adults. Type 1 DM usually has an obvious clinical presentation. Type 2 DM can be asymptomatic for a long time, so tests to screen for Type 2 DM may be needed more frequently.[8] Although fasting plasma glucose and OGTT 2h plasma glucose are the conventional tests for diagnosis, these tests are demanding to apply for both the individual and the institution. On the other hand, HbA1c is relatively simple and feasible. It does not

require fasting and shows less variation.[9] Since it is related to the average glucose level of the last 8-10 weeks, it can provide information about chronic hyperglycemia and complications.[2,3] However, there are also disadvantages. HbA1c may vary according to age and ethnicity.[10] It may show insufficient performance in detecting Type 1 DM, which can develop suddenly. Conditions such as iron deficiency, anemia, and hemoglobinopathy, which change erythrocyte lifespan, may affect HbA1c levels.[11,12]

While fasting and OGTT 2h glucose threshold values were determined in the past, values deviating from the population's normal ranges were used as threshold values; however, currently, it is determined by following diabetes complications.[13] The diagnosis of DM in children is made according to the same criteria used for adults. Although a strong correlation was observed between plasma glucose and HbA1c in adults in many studies, the information on the correlation in children is not clear, since most of these data are based on studies performed on adults.

In the present study, eight (2.1%) individuals were diagnosed with DM. This rate was reported as 1.2% in the previous study, similar to our findings.[8] However, in the study of Kim et al., it was reported as 17.4%.[13] Since the aforementioned study [13] was conducted on individuals who had obesity and/or glycosuria, it is expected that a high rate was found. Some studies conducted in pediatric ages found the diagnostic performance of HbA1c insufficient and was not recommend its use alone.[8,14] In the study by Lee et al.[8] AUC was calculated at a much lower value (0.54) than in the present study to predict dysglycemia (prediabetes or diabetes). Nowicka et al.[14] reported the AUC of Hba1c (0.81) at a similar level to the present study. In the study by Kim et al.[13] the AUCs for each test (fasting glucose, OGTT 2h glucose, and HbA1c) were higher (>0.9) than our findings. However, the performance in the diagnosis of DM, not in the diagnosis of prediabetes, was examined in the aforementioned study.

In prediabetes, the sensitivity of the threshold value of HbA1c≥ 5.7% was low, but it is higher than the sensitivity of OGTT 2h glucose (140 mg/dL), (**Table 2**). In the study of Kim et al.[13] the sensitivities of fasting glucose, OGTT 2h glucose, and HbA1c tests in the diagnosis of pediatric DM were reported as 63.8%, 85.1%, and 89.4%, respectively. In the present study, while the sensitivity of fasting glucose for predicting prediabetes is similar (60.2%), the sensitivities of OGTT 2h glucose and HbA1c tests were much lower (18.1%; 53.0%) than in the mentioned study. In the study of Wallace et al.[15] the sensitivities of Hba1c and fasting glucose were 55.5% and 35.8%, respectively. In this study, 5.7% and 100 mg/dL cut-off values were used, respectively, as in the present study, but it was examined in cases of hyperglycemia (prediabetes or diabetes). Nowicka et al.[14] reported that the optimal threshold of HbA1c was 5.5%, with a specificity of 59.9% and a sensitivity of 57.0%. In the present study, the optimal threshold value was calculated similarly (5.55%), with higher sensitivity and specificity. In previous studies, the sensitivity of blood glucose was reported in the range of 40%-94%.[16,17] The range of these studies using laboratory values of adults is quite wide. The time at which blood is collected (fasting, 1-hour, 2-hour, etc.) may cause differences between studies. Specimen type (serum, plasma, etc.) and type of blood collection tube can affect results. In this study, glucose was analyzed on serum samples. The guideline recommends that glucose be measured in venous plasma if it is used in the diagnosis of diabetes.[18] Although the threshold is determined according to the plasma value, serum samples are also used in many centers. It should be kept in mind that serum glucose values are lower than those of plasma.[19] This means that if glucose is measured in serum, lower values compared to plasma glucose should be used as the cutoff value to achieve similar diagnostic sensitivity. It is also an important issue whether the HbA1c criterion is included when analyses of diagnostic performance are conducted in studies.

In the present study, a low/moderate level of correlation was observed between HbA1c and serum glucose levels. A moderate correlation was observed between fasting and OGTT 2h glucose values. However, Kim et al.[13] and Ogawa et al.[20] reported that glucose levels and the HbA1c test showed a strong correlation. The inconsistencies between the results of the present study and the studies mentioned may be due to the difference in the number of subjects, the difference in ethnicity, and the fact that the studies were conducted on a specific patient group. Because serum glucose levels and HbA1c levels reflect different aspects of glucose metabolism, expecting a one-to-one correlation would be incorrect. For this reason, cases diagnosed according to glucose levels may be missed with HbA1c. The reverse is also possible, meaning that cases diagnosed with HbA1c may be missed by simply looking at glucose levels.

In this study, an HbA1c threshold of 5.55% was determined as the optimal cut-off for diagnosing prediabetes, with 62.7% sensitivity and, 93.0% specificity. An HbA1c threshold of 5.55 can be used for screening prediabetes, and its performance is similar to fasting glucose (≥100 mg/dL). However, the performance of the OGTT 2h glucose (≥140 mg/dL) was as good as neither fasting glucose nor Hba1c. It is not a correct approach to completely exclude the HbA1c test, which is a simple and practically applicable test, in the diagnosis of prediabetes in adolescents. We think that it would be more beneficial to accept HbA1c as a test that can be used together with blood glucose values in prediabetes diagnosis.

CONCLUSION

Although the use of adults' HbA1c criteria for the diagnosis of prediabetes in the pediatric ages is controversial due to the differences between the results of blood glucose and HbA1c-based tests, prediabetes screening is still important.[15] HbA1c

≥ 5.55 will be useful to follow up children in terms of risk and to screen them with blood glucose. The combination of blood glucose and HbA1c tests may reduce the possibility of missing the diagnosis of prediabetes in adolescents.

Due to the retrospective screening of the cases, the inaccessibility of additional disease information that may affect the results and the inability to standardize the preanalytical phase of the tests, especially the OGTT, were among the limitations of the present study.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Van Yüzüncü Yıl University Non-interventional Clinical Researches Ethics Committee (Date: 10.12.2021, Decision No: 2021/13-15).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The author has no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

REFERENCES

1. Cameron FJ, Wherrett DK. Care of diabetes in children and adolescents: controversies, changes, and consensus. Lancet 2015;385(9982):2096-106.
2. Nakagami T, Takahashi K, Suto C, et al. Diabetes diagnostic thresholds of the glycated hemoglobin A1c and fasting plasma glucose levels considering the 5-year incidence of retinopathy. Diabetes Res Clin Pract 2017;124:20-9.
3. Campbell L, Pepper T, Shipman K. HbA1c: a review of non-glycaemic variables. J Clin Pathol 2019;72(1):12-9.
4. American Diabetes Association. 2. Classification and Diagnosis of Diabetes: Standards of Medical Care in Diabetes-2021. Diabetes Care 2021;44(Suppl 1):15-S33. Erratum in: Diabetes Care 2021;44(9):2182.
5. Kapadia CR. Are the ADA hemoglobin A (1c) criteria relevant for the diagnosis of type 2 diabetes in youth? Curr Diab Rep 2013;13(1):51-5.
6. Malkani S, DeSilva T. Controversies on how diabetes is diagnosed. Curr. Opin. Endocrinol. Diabetes Obes 2012;19(2):97-103.
7. Fluss R, Faraggi D, Reiser B. Estimation of the Youden Index and its associated cutoff point. Biom J 2005;47(4):458-72.
8. Lee JM, Gebremariam A, Wu EL, LaRose J, Gurney JG. Evaluation of nonfasting tests to screen for childhood and adolescent dysglycemia. Diabetes Care 2011;34(12):2597-602.
9. Lippi G, Targher G. A laboratory standpoint on the role of hemoglobin A1c for the diagnosis of diabetes in childhood: more doubts than certainties?. Pediatr Diabetes 2011;12(3pt1):183-6.
10. Vikøren TB, Berg JP, Berg TJ. Feilkilder ved bruk av hemoglobin A1c Tidsskr Nor Laegeforen 2014;134(4):417-21.
11. Tarim O, Kucukerdogan A, Gunay U, et al. Effects of iron deficiency anemia on hemoglobin A1c in type 1 diabetes mellitus. Pediatr Int 1999;41:357-62.
12. Klonoff DC. Hemoglobinopathies and Hemoglobin A1c in Diabetes Mellitus. J Diabetes 2020;14(1):3-7.
13. Kim MS, Jo DS, Lee DY. Comparison of HbA1c and OGTT for the diagnosis of type 2 diabetes in children at risk of diabetes. Pediatr Neonatol 2019;60(4):428-34.
14. Nowicka P, Santoro N, Liu H, et al. Utility of hemoglobin A(1c) for diagnosing prediabetes and diabetes in obese children and adolescents. Diabetes care 2011;34(6):1306-11.
15. Wallace AS, Wang D, Shin JI, et al. Screening and Diagnosis of Prediabetes and Diabetes in US Children and Adolescents. Pediatrics 2020;146(3):e20200265.
16. Kaur G, Lakshmi P, Rastogi A, et al. Diagnostic accuracy of tests for type 2 diabetes and prediabetes: A systematic review and meta-analysis. PloS one 2020;15(11):e0242415.
17. Jagannathan R, Sevick MA, Fink D, et al. The 1-hour post-load glucose level is more effective than HbA1c for screening dysglycemia. Acta diabetologica 2016;53(4):543-50.
18. Kim HS. Blood Glucose Measurement: Is Serum Equal to Plasma? Diabetes Metab J 2016;40(5):365-6.
19. Frank EA, Shubha MC, D'Souza CJ. Blood glucose determination: plasma or serum?. J Clin Lab Anal 2012;26(5):317-20.
20. Ogawa E, Urakami T, Suzuki J, Yoshida A, Takahashi S, Mugishima H. Usefulness of HbA1c to diagnose diabetes among Japanese children detected by a urine glucose screening program in the Tokyo Metropolitan Area. Endocr J 2012;59(6):465-71.