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REVIEW / PRACA POGLĄDOWA

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1,5-ANHYDROGLUCITOL (1,5-AG) AND ITS USEFULNESS IN CLINICAL PRACTICE

1,5-ANHYDROGLUCITOL (1,5-AG) I JEGO ZASTOSOWANIE W PRAKTYCE KLINICZNEJ

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S u m m a r y

1,5-anhydroglucitol (1,5-AG) is a major polyol in human serum, structurally similar to D-glucose. The 1,5-AG pool can be determined by the balance between oral intake and urinary excretion. It is derived mainly from dietary sources with a half-life of about 1-2 weeks. 1,5-AG is not metabolized, whereas it is excreted in urine and nearly 99.9% of it is reabsorbed by the kidneys. When serum glucose level exceeds the renal threshold for glucosuria, urinary glucose suppresses tubular reabsorbing of 1,5-AG, leading to a loss of it in the urine and a rapid reduction of this polyol in serum levels. Therefore, the plasma 1,5-AG concentration indirectly reflects episodes of hyperglycaemia. This marker can be measured in serum, EDTA or in plasma using enzymatic assays or chromatography techniques which are also helpful to detect 1,5-AG in urine.

In clinical practice, 1,5-AG is a good marker of short-term episodes of hyperglycaemia such as postprandial hyperglycaemia and other short term glycaemia excursions, for example during pregnancy or in pre-conception, before operations and after glycaemia-related therapeutic changes. It has been also reported as a marker of first-ever cardiovascular disease, a clinical test to differentiate subtypes of diabetes and to monitor type 1 diabetes in children. Despite small limitations such as end-stage renal disease or liver cirrhosis, which should be taken into consideration when interpreting levels of 1,5-AG, it seems to be a useful and sensitive marker of acute and postprandial hyperglycaemia episodes in diabetology or cardiodiabetology.

S t r e s z c z e n i e

1,5-anhydroglucitol (1,5-AG) jest głównym poliolem występującym w ludzkiej surowicy, podobnym strukturalnie do D-glukozy. Na całkowitą jego pulę w ustroju wpływa zachowanie równowagi między podażą w diecie a wydalaniem. Podstawowym źródłem 1,5-AG w organizmie jest pokarm, zaś okres półtrwania tego związku waha się w granicach od 1 do 2 tygodni. 1,5-AG nie podlega metabolizmowi i jest wydalany przez nerki, gdzie ulega zwrotnej reabsorpcji w prawie 99,9%. Kiedy poziom glikemii we krwi przekracza próg nerkowy, glukoza kompetycyjnie hamuje reabsorpcję nerkową 1,5-AG, co powoduje jego utratę z moczem i obniżenie stężenia w surowicy. Dlatego uważa się, że poziom 1,5-AG dokładnie odzwierciedla epizody hyperglikemii. Marker ten może być oznaczany w surowicy, EDTA i osoczu przy zastosowaniu metod enzymatycznych lub chromatograficznych, które także są pomocne w wykrywaniu 1,5-AG w moczu. W praktyce klinicznej 1,5-anhydroglucitol jest dobrym markerem krótkotrwałych epizodów hiperglikemii, takich jak hiperglikemia poposiłkowa, czy innych krótkotrwałych zwyżkek poziomu glukozy we krwi np. obserwowanych w trakcie ciąży, w okresie przedkoncepcyjnym lub przed planowanymi zabiegami operacyjnymi. Jest także przydatny w szybkiej ocenie modyfikacji leczenia cukrzycy. Opisuje się również zastosowanie oznaczania stężenia 1,5-AG jako niezależnego markera ryzyka sercowo-naczyniowego, parametru ułatwiającego diagnostykę różnicową typów cukrzycy i pozwalającego na monitorowanie leczenia cukrzycy typu 1 u dzieci. Pomimo pewnych ograniczeń w stosowaniu, takich jak niewydolność nerek czy marskość wątroby, które powinny być wzięte pod uwagę w interpretacji stężenia 1,5-AG, związek ten wydaje się być przydatnym i wrażliwym markerem epizodów ostrej i poposiłkowej hiperglikemii, mogącym dostarczyć cennych informacji w praktyce diabetologicznej i kardiodiabetologicznej.

Key words: 1,5-anhydroglucitol, postprandial hyperglycaemia, acute hyperglycaemia, diabetes, cardiovascular risk
Słowa kluczowe: 1,5-anhydroglucitol, hiperglikemia poposiłkowa, ostra hiperglikemia, cukrzyca, ryzyko sercowo-naczyniowe

INTRODUCTION

1,5-anhydroglucitol (1,5-AG) is a naturally occurring monosaccharide, structurally identical to D-glucose except for the absence of the C-1 hydroxyl group [1]. Comparison of D-glucose and 1,5-anhydroglucitol was demonstrated on Figure 1 [2]. It is a major polyol in human serum [3]. While its metabolic role is still unclear in mammalian cells, it is known that free 1,5-AG is found in all organs and tissues (1,5-AG pool), with the total amount several times higher than of that in plasma. The 1,5-AG pool can be determined by the balance between oral intake and urinary excretion, although there is a small amount of the novo synthesis [2, 4]. 1,5-AG is derived mainly from dietary sources and has a large storage pool in all tissues [1]. 1,5-AG levels are extremely stable in euglycemic individuals and are not affected by prandial state, body weight or age [5]. The nonmetabolizable glucose analogue is reabsorbed by the kidneys in nearly 99.9% [2]. It is known that glucose can inhibit tubular reabsorption of 1,5-AG during periods of hyperglycemia [6].

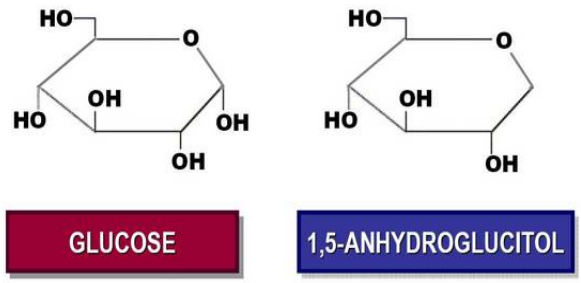

Fig. 1. *Comparison of D-glucose and 1,5-anhydroglucitol [2]*
Ryc. 1. *Porównanie D-glukozy i 1,5-anhydroglucitolu [2]*

There is an increasing evidence that postprandial hyperglycemia is a risk factor for the development of macroangiopathic complications of diabetes [7]. It is suggested that serum 1,5-AG level reflects glycemic control and shows sensitively changes in plasma glucose levels, and can reflect postprandial hyperglycemia [3].

HISTORICAL CONTEXT OF 1,5-ANHYDROGLUCITOL

1,5-AG was discovered and isolated in 1888 from *Polygara amara* plant by Chodat. Many years later, in 1943 its chemical structure was defined [2, 8]. In 1975 Pitkänen first reported on the existence of 1,5-AG in human plasma and cerebrospinal fluid in diabetic patients; at that time first studies showed low levels of 1,5-AG in patients with diabetes but first commercial assay was done in Japan in 1991 [9].

1,5-anhydroglucitol has been widely studied in Japan and in USA. Moreover it received US FDA approval for short-term glycemic monitoring in 2003 [2,8].

PHYSIOLOGY OF 1,5-AG

Dietary 1,5-AG intake is estimated to be 4.0-5.5mg/day and the polyol is well absorbed in the intestine. Free 1,5-AG is believed to be present in all organs and tissues (1,5-AG pool) and its amount has been reported to be about 500-1000mg [9,10]. Only a small rate of 1,5-AG (0,5mg/day) is synthesized de novo, probably by the liver [6,10]. All intake is balanced by urinary excretion and nearly 99.9% is reabsorbed by the kidneys at a specific sodium glucose active cotransporter (SGLT4) [2,11]. The reference values of 1,5-AG plasma levels in healthy human subjects range from 12 to 40µg/ml and its half-life is 1-2 weeks [12]. In diabetics, its level is markedly reduced, for example in patients with type 2 diabetes it varies between 0.9-26.6µg/ml [13]. The most characteristic features of 1,5-AG is: inert metabolism-the portion of 1,5-AG ingested with food within a day is balanced by the portion which is eliminated from the body at the same time and entire elimination by the kidneys. That is why, there is a stable concentration of 1,5-AG in plasma in healthy persons within 24 hours and rapid elimination of it by the kidneys when the renal threshold for glucose is exceeded [8, 14]. When serum glucose level exceeds the renal threshold for glucosuria (typically >180mg/dl), urinary glucose suppresses reabsorption of 1,5-AG via SGLT4 at proximal tubules of kidney, leading to a loss of 1,5-AG in the urine and a rapid reduction of this polyol in serum levels [2, 11, 15]. Owing to this relationship, the plasma 1,5-AG level indirectly reflects episodes of hyperglycemia. At the onset of glucosuria due to hyperglycaemic episodes, the plasma 1,5-AG level promptly falls in direct proportion to the severity of glucosuria [13, 16]. When normoglycaemia is restored, 1,5-AG recovers at 0.3µg/ml/day and it may take even 5 weeks [2, 12, 14]. The decrease of 1,5-AG concentrations occurs faster than its increase during improvement of glycaemic control [8, 11].

SOURCES OF 1,5-ANHYDROGLUCITOL. THE ROLE OF DIET AND LIVER FUNCTION ON SERUM 1,5-AG LEVELS

The amounts of 1,5-AG produced endogenously are not significant and the main source of 1,5-AG in human body is food [14]. Although it is suggested a functional role of the liver in 1,5-AG synthesis, some reports observed the synthesis of 1,5-AG by cultured cells of rat hepatoma cell line.

Additionally, serum 1,5-AG concentrations are significantly lower in cirrhotic patients independently of plasma glucose levels than in healthy controls.1,5-AG level is positively correlated with both serum cholinesterase and albumin levels [17].

The largest food source is soy, small quantities are present in rice, pasta, meats, fish, fruit, vegetables, tea, milk and cheese [2]. It is suggested that ordinary diet does not affect 1,5-AG concentrations but some studies report the differences in 1,5-AG level across ratial/ethnic groups. Asians and Africans have significantly higher baseline mean 1,5-AG compared with Caucasians [18].On the other hand, small studies in Japan have found little influence of daily food intake on serum 1,5-AG levels, which may be attributed to the relatively large body pool of 1,5-AG [15]. Kawasaki et al. [10] and Dungan [2] reported higher concentration of 1,5-AG after taking the traditional Chinese herbal medicine (Kampo), because it contains large amounts of 1,5-AG (*Polygalae radix*, which is the crude element of Kampo, belongs to *Polygalaceae*). These differences within ethnic groups do not negate the utility of 1,5-AG in use. It is needed to perform separate ranges of 1,5-AG level for particular populations [7].

Furthermore, intravenous hyperalimentation and total enteral nutrition diet may increase 1,5-AG due to high concentration 1,5-AG of them [10].

THE METHODS FOR THE DETERMINATION OF 1,5-AG IN BLOOD AND IN URINE

1,5-anhydroglucitol can be measured in serum, EDTA plasma or in urine. In blood samples 1,5-AG is stable at 2-8°C for 7 days and at 22°C for 5 days. Samples can be frozen long-term at -80°C; 1,5-AG can withstand at least three freeze-thaw cycles at -80°C [19]. Shipment of samples should be on ice or on dry ice in case of long distances [19].

Blood levels of 1,5-AG are typically measured using either a commercially available enzymatic kit, gas chromatography-mass spectrometry (GC/MS) or high-performance liquid chromatography (HPLC) [5]. There are two enzymatic assays for blood 1,5-AG: Glyco-Mark™ (GlycoMark, Inc) used in USA and Determiner-L (Kyowa Medex, Tokyo) approved in Japan [20].

Although these two 1,5-AG assays give slightly different results in the same samples due to disagreements in calibration, recent data suggest that they are comparable and can be used interchangeably [20]. The enzymatic methods are convenient and not laborious; they can be used on automated chemistry analyzers such as Hitachi 917. Only 1ml of blood sample volume is recommended to measure 1,5-AG concentration and fasting is not required [19].

The Glyco-Mark™ assay is a 2-step method consisting of a 2-reagent system. In the first step, the specimen is incubated with a reagent mixture (glucokinase, pyruvate kinase, phosphoenol pyruvate) that converts endogenous glucose to glucose-6-phosphate in order to avoid its interference with the second enzymatic step [2, 5]. The second reagent (pyranose oxidase) oxidizes 1,5 AG, producing hydrogen peroxide H2O2. Peroxidase catalyzes the formation of a colored end product from

4-aminoantipyrine and TOOS (N-ethyl-N-(2-hydroxy-3-sulfopropyl)-3-methylaniline sodium dehydrate) with the absorbance measured at 546 nm Detection limits of the assay are approximately 0.3mg/l based on 0.5ml of serum [5, 20].

In the Kyowa Medex assay, 1,5-anhydro-D-glucitol (1,5AG) is first converted into 1,5-anhydro-glucitol-6-phosphate (AG-6-P) by ADP dependent hexokinase (ADP-HK) and adenosine-5 -diphosphate (ADP). AG-6-phosphate dehydrogenates (AG6P-DH) reacts with AG-6-P and acid β-NADP+, producing β-NADPH. Diaphorase (DIP), then promotes the reaction of NADPH, and the tetrazolium salt 2-(4-iodophenyl)-3-(4-nitrophenyl)-5-(2,4-disulfo-phenyl)-2H-tetrazoliumsodium to produces a water-soluble formazan pigment, measured at 450 nm to determine the 1,5-AG concentration [20].

Alternatively, 1,5-AG in serum may be measured using chromatography techniques. These methods are sensitive and precise, but can also be time-consuming and cumbersome [2].

Analysis of 1,5-AG by gas chromatography-mass spectrometry (GC/MS) requires labor intensive sample

preparation (typically protein precipitation or protein precipitation coupled with ion-exchange chromatography) followed by derivatization, typically via acetylating [5].

High-performance liquid chromatography (HPLC) analysis of 1,5-AG in serum has been also reported. 1,5-AG concentration in blood has been determined by passing the samples through a 2- or 3-layer ion exchange column and then analyzing by HPLC with pulsed amperometric detection or an enzyme sensor. Typical detection limits for 1,5-AG in this method were reported between 100 and 200ng/ml [5].

Niwa et al. [21] analyzed 1,5-AG in serum using cation-exchange chromatography and liquid - chromatography mass spectrometry (LC/MS). In this method 1,5-AG was monitored as its chloride adducts using an atmospheric pressure chemical ionization source (APCI) in the negative ionization mode. Detection limits of the assay are approximately 0.5ml of serum and 200ng/ml for 1,5-AG [5].

A more sensitive method is needed for the analysis of 1,5-anhydroglucitol in urine, where levels are significantly lower than in plasma. Some reports documented detection limits of 1,5-AG in urine as low as 0.06µg/ml based on 0.1-0.2ml of urine [5].

HPLC analysis can also be used to detect 1,5-anhydroglucitol in urine. Oxidation by pyranose oxidase producing hydrogen peroxide (the basis of the Glyco-Mark™ assay) was also applied to the HPLC platform to determination of 1,5-AG in urine [5]. The limits are the same as in serum.

Onorato et al. [5] described liquid chromatography and ion trap mass spectrometry (LC/MS3) assay, as a sensitive and selective method of determination of 1,5-AG in urine. They used diluted human urine samples and analyzed them by LC/MS3 with an APCI source operated in the negative ionization mode. Use of an ion trap allowed monitoring MS3 transitions for both 1,5-AG and the internal standard which provided sufficient selectivity and sensitivity for analysis from 50µl of human urine. Quantitation of 1,5-AG levels in urine was accomplished using a calibration curve generated in water (calibration range 50ng/ml to 10µg/ml) [5].

THE APPLICATION OF 1,5-ANHYDROGLUCITOL IN CLINICAL PRACTICE

1,5-AG as a marker of postprandial hyperglycemia and short-term glycemic status

HbA1C is regarded as the gold standard index of glycemic control in patients with diabetes but does not discriminate between relative contributions of fasting plasma glucose and postprandial glycemia to mean glycemia. Moreover, HbA1C is not a good indicator of glycemic control over shorter periods or of glucose excursions [2,16,22]. HbA1C and fructosamine reflect time-averaged glycaemia in the past 2-3 months and in the past 2-3 weeks, respectively. 1,5-AG measurements mirror glycemic status over the previous 48h to 2 weeks [14,22]. Serum 1,5-anhydroglucitol is well-known to be a useful clinical marker of both short-term glycemic status and postprandial hyperglycemia [2, 8, 23]. Some researchers maintained that this assay would be clinically useful for monitoring short-term glycaemia changes, such as preoperatively, pre-conception, in pregnancy and after glycaemia-related therapeutic changes [12]. Stettler et al. [18] suggested that 1,5-AG might be used as a substitute for postprandial glucose measurements, complementing HbA1C and fructosamine measurements [8,18,22]. Comparison of glycaemic markers is shown in Table I [2].

Table I. *Comparison of glycemic markers [2]*
Tabela I. *Porównanie markerów glikemii [2]*

PARAMETER	HbA1C	FRUCTOSAMINE	1,5-AG
Time required for significant change	1-3 months	1-2 weeks	1-3 days
Reflection of mean glucose	++	++	+
Reflection of glucose excursions/postprandial glucose	+	+	++
Greatest degree of change is found during	Moderate-to-severe hyperglycemia	Moderate-to-severe-hyperglycemia	Mild-to-moderate hyperglycemia

1,5-AG is a useful index in patients with relatively well-controlled diabetes and it is suggested that 1,5-AG might be a complementary tool to HbA1C for monitoring the trend of glucose excursion in patients with moderately controlled type 2 diabetes [2,7,16].

1,5-AG as a marker of first-ever cardiovascular disease

Previous epidemiological studies have shown that an increased postload glucose level in an oral glucose tolerance test (OGTT) is an independent risk factor for the development of macrovascular complications such as cardiovascular disease (CVD) because hyperglycemia is a risk for atherosclerotic disease and is a reflection of insuline resistance which is closely related to its risk factors [7,16,23]. It is important to predict postprandial hyperglycemia in the early stages of glucose intolerance [7,8]. Measurement of 1,5-AG concentrations can detect not only patients with

persistent hyperglycemia but also those with transient postprandial hyperglycemia who are likely to be at higher risk for development diabetes in the future [23]. Some reports indicated that in patients with acute coronary syndrome, 1,5-AG may be useful in discriminating those with stress hyperglycemia from normoglycemic subjects [2]. Watanabe et al. [23] suggested that measurement of serum 1,5-AG levels is useful to detect individuals, especially men, at higher risk of CVD, regardless of the presence or absence of diabetes. Moreover, measurement of serum 1,5-AG can be performed easily with a single non-fasting blood sample and its level is not affected by red cell turnover and hemoglobinopathies [23].

1,5-AG as a clinical test to differentiate subtypes of diabetes

Pal et al. [24] described 1,5-AG as a clinical marker in discriminating maturity-onset diabetes of the young due to HNF1A mutations (HNF1A-MODY) from type 2 diabetes and GCK-MODY. Making the correct molecular diagnosis allows individualization of treatment; HNF1A-MODY is needed to be treated of low dose sulfonylurea as a first line. Also, important information about prognosis and guidelines investigation of family members can be done [24]. Molecular genetic testing is currently too expensive for indiscriminate use; thus 1,5-AG could inform decisions regarding it. It is known that HNFA1 mutations are characterized by low renal glucose threshold due to decreased expression of the high-affinity low capacity glucose co-transporter 2 (SGLT2) [24]. Previous study in Polish subject found that mean 1,5-AG concentrations were 50% lower in patients with HNF1A-MODY compared with those with type 2 diabetes [25].

Koga et al. [11] reported that measurement of 1,5-AG is useful to discern fulminant type 1 diabetes (FT1DM) from type 2 diabetes. Serum 1,5-AG levels were lower in the FT1DM patients than in type 2 diabetes patients. FT1DM characterizes clinically by acute and almost complete pancreatic β cell destruction without anti-GAD and anti-IA-2 autoantibodies but plasma glucose is markedly elevated; HbA1C levels is normal or only slightly higher [11]. The diagnosis is very important in order to start insulin treatment to avoid abrupt deterioration and poor prognosis [11].

1,5-AG for monitoring type 1 diabetes in children

The reference ranges for 1,5-AG in normal children and in children with type 1 diabetes are not known. However, Nguyen et al. [26] reported a statistically significant difference in 1,5-AG concentrations between these two groups. In this study, the range of 1,5-AG in normal children was 15.6-29.2μg/ml but in children with type 1 diabetes it was lower: 1.6-10.9μg/ml. It indicates that there is a concordance with reports in adult patients [8,26]. That is why, it is suggested that plasma 1,5-AG concentrations may be used in the future to evaluate therapy, especially to target postprandial hyperglycemia in children with type 1 diabetes and near normoglycaemia [2,26].

1,5-AG as an indicator of hyperglycemic excursions in pregnancy

It has been well documented that disturbances in carbohydrate metabolism observed during pregnancy result in numerous serious complications of fetal development such as fetal macrosomy, abnormalities in fetal growth and central nervous system development, organomegaly, immaturity of the respiratory system and in addition neonatal hypoglycemia. Furthermore, inadequate treatment of diabetes leads to increased rates of perinatal mortality and morbidity in mothers and neonates [13]. As well frequent self-monitoring of blood glucose as routinely used long-term markers of the overall glycaemic state such as HbA1C and fructosamine do not reveal every acute hyperglycaemic spike which can be reflected in 1,5-AG concentrations [2,13]. It is known that renal function during pregnancy is characterized by significant changes in filtration and tubular reabsorption, dependent on gestational age and the time of a day [13]. In addition, in pregnant women there is a dilutional effect caused by rise in plasma volume [1]. Tetsuo et al. [27] suggested that a change in 1,5-AG plasma level may reflect a mild alteration of carbohydrate metabolism, other authors concluded that differences in renal glucose threshold between patients limit the usefulness of this marker in pregnant women [2,8,13]. Dworacka et al. [13] suggested that the variation in renal threshold for glucose is the important limitation for the use of 1,5-AG for diabetes screening, but not for diabetes monitoring; 1,5-AG may serve as a useful tool of daily glucose excursion in pregnant women with diabetes, as an adjunct to HbA1C monitoring and can provide valuable information regarding effectiveness of treatment.

THE INFLUENCE OF KIDNEY DISEASES ON 1,5-AG CONCENTRATIONS

Plasma 1,5-AG concentrations must be interpreted with caution in patients with renal dysfunction because its level depends on renal threshold for glucose and tubular function [2,19,26]. For instance, 1,5-AG concentration decreases in adult patients with chronic renal failure and with end-stage renal disease in patients with or without diabetes [26]. Some authors suggested that 1,5-AG may be useful in those with mild renal disease who have some albuminuria, however not in those with proteinuria [8]. Moreover, peritoneal dialysis and hemodialysis lower the plasma 1,5-AG level [26]. Fujisawa et al. [28] demonstrated that renal tubular function affects the urinary excretion of 1,5-AG and modifies the plasma 1,5-AG level in patients with diabetes. In addition, urinary excretion of 1,5-AG and urinary β2-microglobulin are positively correlated [28].

OTHER CONDITIONS WHICH ADVERSALY AFFECT 1,5-AG CONCENTRATIONS

There is very little interference from triglyceride and uric acid; high hypertriglyceridaemia (>30mmol/l) and hyperuricemia (>20mg/dl) may affect serum 1,5-AG level. Decreased 1,5-AG concentrations are observed in patients after gastrectomy and during steroids therapy [12,19].

α-glucosidase inhibitors such as acarbose, which delay the breakdown of carbohydrate in the small intestine, and thus diminish the postprandial rise of blood glucose in diabetic subjects, not only do not increase, but rather can decrease serum 1,5-AG level in those patients [8]. At the same time, other clinical markers of glycemic control have been improved. Watanabe et al. [4] suggested that the lack of increase of 1,5-AG after treatment with acarbose might be due to reduced 1,5-AG absorption from the small intestine resulting from inhibition of alpha-amylase.

CONCLUSIONS

1,5-anhydroglucitol is a sensitive and useful marker of short-term episodes of postprandial and acute hyperglycemia, which might be missed in standard used assays such as self-monitored blood glucose or HbA1C and fructosamine. Despite small limitations, which should be taken into consideration when interpreting levels of 1,5-AG, there are potential possibilities to use this polyol in clinical practice. Continuous research will allow its new applications in the future, especially in cardiodiabetology.

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