GLYCEMIC MONITORING OF BRAZILIAN ADOLESCENTS WITH TYPE 1 DIABETES

MONITORIZACIÓN GLICÉMICA DE ADOLESCENTES BRASILEIROS CON DIABETES TIPO 1

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ABSTRACT

Objective: to verify the methods used by Brazilian adolescents with DM1 in glycemcic monitoring and concepts associated with this practice. Method: integrative review, carried out between February and August of 2017, through MEDLINE, LILACS and SCIELO. The analysis of the studies considered the level of evidence. The results were presented considering the decreasing chronological sequence and the themes coming from the analysis of the articles. Results: the themes “1. Perspectives of studies on Type 1 Diabetes Mellitus (DM1) in adolescents in Brazil”; “2. Monitoring of glycemia in Brazilian adolescents with DM1: concepts and methods” and “3. The role of primary measurement techniques for the control of DM1 in adolescents” were observed. Conclusion: it is pointed out that the analysis of Glycosylated Hemoglobin A (HbA1c) was the most used method for the monitoring of adolescents with DM1. It is also verified that there are difficulties of the scientific community to include children and adolescents with DM1 in experimental studies. Descriptors: Adolescent; Insulin; Blood Glucose Self-Monitoring; Hemoglobin A, Glycosylated; Diabetes Mellitus, Type I, Health Education.

RESUMO

Objetivo: verificar os métodos utilizados por adolescentes brasileiros com DM1 na monitorização glicêmica e conceitos associados a essa prática. Método: revisão integrativa, realizada entre fevereiro a agosto de 2017, por meio da MEDLINE, LILACS e SCIELO. A análise dos estudos considerou o nível de evidência. Os resultados foram apresentados considerando a sequência cronológica decrescente e as temáticas advindas da análise dos artigos. Resultados: observaram-se as temáticas “1. Perspectivas de estudos sobre Diabetes Mellitus Tipo 1 (DM1) em adolescentes no Brasil”; “2. Monitorização da glicemia em adolescentes brasileiros com DM1: conceitos e métodos” e “3. O papel das técnicas de mensuração primária para o controle do DM1 em adolescentes”. Conclusão: aponta-se que a análise da Hemoglobina A Glicosilada (HbA1c) foi o método mais empregado para a monitorização de adolescentes com DM1. Verifica-se, também, que há dificuldades da comunidade científica em incluir crianças e adolescentes com DM1 em estudos experimentais. Descriptores: Adolescent; Insulina; Automonitoreo de la Glicemia; Hemoglobina A Glicosilada; Diabetes Mellitus Tipo I; Educação em Saúde.

RESUMEN

Objetivo: verificar los métodos utilizados por adolescentes brasileños con DM1 en la monitorización glucémica y conceptos asociados a esta práctica. Método: revisión integrativa, realizada entre febrero a agosto de 2017, por medio de MEDLINE, LILACS y SCIELO. El análisis de los estudios consideró el nivel de evidencia. Los resultados fueron presentados considerando la secuencia cronológica decreciente y las temáticas provenientes del análisis de los artículos. Resultados: se observaron las temáticas: “1. Perspectivas de estudios sobre Diabetes Mellitus Tipo 1 (DM1) en adolescentes en Brasil”; “2. Monitoreo de la glucemia en adolescentes brasileños con DM1: conceptos y métodos”; y “3. El papel de las técnicas de medición primaria para el control del DM1 en adolescentes”. Conclusión: se señala que el análisis de la Hemoglobina A Glicosilada (HbA1c), fue el método más empleado para la monitorización de adolescentes con DM1. Se verifica, también, que hay dificultades de la comunidad científica en incluir niños y adolescentes con DM1 en estudios experimentales. Descriptores: Adolescentes; Insulina; Automonitoreo de la Glicemia; Hemoglobina A Glicosilada; Diabetes Mellitus Tipo I; Educación en Salud.
INTRODUCTION

DM1 is characterized by the destruction of pancreatic \( \beta \) cells, generally leading to absolute insulin deficiency. It corresponds to 90% of cases of diabetes in childhood and has, as a world prevalence, about 500 thousand children under 15 years. Three-quarters of cases of DM1 are diagnosed at age 18.\(^1\) The countries with the highest estimated number of new cases were the United States (13,000 new cases), India (10,900 new cases), and Brazil (five thousand new cases cases).\(^1\)

The DM1 adolescent, due to biological changes (height / age, hormonal changes and puberty) and psychosocial (greater independence and maturity), may face challenges to control the disease. The biological changes of adolescence are responsible for the hyperactivity of the growth hormone secretion, which increases the resistance of glucose metabolism, since it is stimulated by insulin, reflecting in greater difficulty in establishing glycemic control. Through the physiological changes, glycemic monitoring becomes essential to obtain adequate levels of glucose in this group and is indicated as an effective practice in metabolic (or glycemic) control.\(^4\)

Two primary techniques are available for health professionals and patients to perform glycemic excursions and their control: blood glucose self-monitoring (AMG), also known as self-monitoring of blood glucose (SMBG), obtained by capillary glycemia (CG) and measurement of interstitial glucose by the Continuous Glucose Monitoring System (CGMS). Both can be performed at the patient's home. There is also the evaluation of glycated hemoglobin A (or HbA1c), which is performed laboratorially.\(^1,5^6\)

SMBG represents an integral component of effective diabetes therapy allowing patients to assess whether glycemic targets are being reached and increasing their daily frequency has been associated with lower levels of HbA1c in children and adolescents.\(^1\)

It is recommended that services that serve adolescents with DM1 provide a trained multiprofessional team composed of physicians, nutritionists and diabetes / pediatrics specialist nurse.\(^4\) As the nurse performs the individualized care plan, the need for prior knowledge of this professional about glycemic monitoring in adolescents with DM1 is fundamental.

OBJECTIVE

- To verify the methods used by Brazilian adolescents with DM1 in glycemic monitoring and concepts associated with this practice;
- Classify articles on the level of evidence and present potential limitations / biases.

METHOD

Integrative review that adopted the following phases: 1º. Phase - elaboration of the guiding question; 2º. Phase - search or sampling in the literature; 3º. Phase - data collection; 4º. Phase - critical analysis of included studies; 5th. Phase - discussion of results; 6º. Phase - presentation of the integrative review.

The following guiding question was formulated: what methods of glycemic monitoring are used in Brazilian adolescents with DM1? The construction of the research question considered the PICO strategy, which represents an acronym for Patient, Intervention, Comparison and Outcomes. Through the strategy, 'P' refers to patients with T1DM restricting themselves to adolescents and the 'I' referred to the drug intervention for the treatment of DM1, ie, insulin. The "C" referred to self-monitoring of blood glucose and "O" referred to the result of each method through the levels of HbA1c.

The search for articles occurred between February and August of 2017 using the descriptors controlled by the Health Sciences Descriptors (DeCS-BIREME) and Medical Subject Headings (MeSH-Medline). The terms were: "Adolescent"; "Insulin"; "Glucose self-monitoring" and "glycosylated hemoglobin A"; "Adolescent"; "Insulin"; "Blood glucose self-monitoring" and "Hemoglobin A, glycylated".

When considering the PICO strategy, the descriptors were defined as follows: \( P = \) (adolescent); \( I = \) (insulin); \( C = \) (self-monitoring of blood glucose) and \( O = \) (glycosylated hemoglobin A). With the boolean operator selected AND, the search was performed using the combination: (insulin) AND (glucose self-monitoring) AND (adolescents) AND (glycosylated hemoglobin A). The search strategy considered the combinations of the above descriptors: \( P \) AND \( I \) AND \( C \) AND \( O \).

In Medline, the beta version was used for the direct insertion of the components of the PICO strategy.8 Articles can be observed according to the database in Figure 1.
After the search, 271 articles were found, of which 261 were available in MEDLINE and ten in LILACS. In view of this total, the criteria for inclusion were applied: national articles that included adolescents with DM1 as subjects of research and articles published between July 2005 and July 2017. Duplicate articles were excluded and those that were not available in full.

The titles and summaries of the 271 articles were read to verify compliance with the inclusion criteria. The preliminary analysis adopted a validated instrument that allowed the obtaining of information such as: subjects of the research, design and characteristics of the study, as well as theoretical-methodological coherence. Six articles were read in full to verify compliance with the objectives of the study. After reading the full articles, it was verified that five articles answered the question of this review.

The articles were classified according to the methodological quality and bias of the articles, as well as by the level of evidence proposed by Souza, Silva and Carvalho. For the analysis of the methodological quality and bias of the articles, the adapted instrument Critical Appraisal Skills Program (CASP) 10, which classifies the articles into two categories: level A - six to ten points (articles with good methodological quality and reduced bias) and level B - minimum of five points (satisfactory methodological quality, however, with increased risk of bias). At the end of the evaluation, all articles were considered as level A, remaining in the sample.

Regarding the level of evidence, it was classified as: level 1 - evidence resulting from the meta-analysis of multiple controlled and randomized clinical studies; level 2 - evidences obtained in individual studies with experimental design; level 3 - evidence from quasi-experimental studies; level 4 - evidence from descriptive (non-experimental) studies or qualitative approach; level 5 - evidence from case or experience reports and level 6 - evidence based on expert opinions.

After the qualification process, information was extracted on the title, place, year, study design and level of evidence according to the theoretical reference adopted. Figure 2 presents the synthesis of the characteristics of the articles selected for this integrative review.
Quantitative analysis was also performed on the availability of the article in the selected electronic address, level of evidence of the studies regarding the theoretical reference and glycemic monitoring methods used. The quantitative analysis comprised the description of the absolute and relative frequencies elaborated through the program Microsoft Excel, version 2015.

After analyzing the articles, they were discussed and compared with the theoretical framework for glycemic monitoring in diabetes. The presentation of this review considered the categorization of the articles by decreasing chronological sequence and themes that arose after the analysis of the collected data.9

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**RESULTS**

The search for articles through the PICO strategy, in the selected electronic addresses, resulted in 271 articles. When the criteria one and two were applied and articles were duplicated, the result was five articles for the analysis. Of these, four (80%) were available in LILACS, and one (20%) in MEDLINE. Regarding the level of evidence of the selected papers, four (80%) presented level of evidence four and one (20%), level three. There were no studies of levels one, two, five and six. Figure 3 presents the limitations / biases of the selected articles that composed this review.

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<table>
<thead>
<tr>
<th>Code</th>
<th>Limitations/bias</th>
</tr>
</thead>
<tbody>
<tr>
<td>A1</td>
<td>Absence of autoantibodies and C-peptide measurement of the participants, allowing the inclusion of other types of diabetes in the study. In this study, patients from the secondary and tertiary care networks were included, not allowing the analysis of data from the primary health care network.</td>
</tr>
<tr>
<td>a2</td>
<td>Absence of glycemic excursion in the morning shift.</td>
</tr>
<tr>
<td>a3</td>
<td>Not reported / evidenced.</td>
</tr>
<tr>
<td>a4</td>
<td>Not reported / evidenced.</td>
</tr>
<tr>
<td>a5</td>
<td>Statistical limitation due to the small number of patients analyzed and they served as a control group.</td>
</tr>
</tbody>
</table>

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Figure 2. Synthesis of articles included in the integrative review. Natal (RN), Brazil, 2017.

Figure 3. Articles listed in chronological order, considering limitations / biases. Natal (RN), Brazil, 2017.
Figure 4 provides information on the objectives, methods of glycemic analysis and study outcomes.

<table>
<thead>
<tr>
<th>Code</th>
<th>Objective</th>
<th>Glycemic monitoring method</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>a1</td>
<td>To evaluate the economic influence on the care of Brazilian adolescents with DM1, according to the American Diabetes Association (ADA).</td>
<td>HbA1c</td>
<td>75% of patients with very low economic status had HbA1c levels above the target, that is, with 23.2%. The frequency of self-monitoring was associated with the economic level of each patient, resulting in low or non-existent patients with a very low economic level.</td>
</tr>
<tr>
<td>A2</td>
<td>To assess the impact of Silent Hypoglycemia (HS) time on glycemic control of type 1 diabetic patients under continuous glucose monitoring.</td>
<td>GC and the Continuous Glucose Monitoring System (CGMS)</td>
<td>Monitoring by CGMS detected more glycemic excursions than CG. HS is more durable at night than in the daytime period. It was also observed lower glycemic mean the longer the time of hyperglycemia.</td>
</tr>
<tr>
<td>A3</td>
<td>Check existing diabetes education guidelines and guidelines, recommendations for program adaptation by age range, and effect of education programs on HbA1c levels.</td>
<td>HbA1c</td>
<td>There is no universally recognized universal diabetes education program. The proper self-monitoring of the GC is a measure proposed by the American Association of Diabetes Educators (AADE). When compared to GC, CGMS provides intermittent glycemic control data, detecting inter and postprandial and / or nocturnal variations. It is the only continuous glucose monitoring system commercially available in Brazil.</td>
</tr>
<tr>
<td>A4</td>
<td>To evaluate how CGMS can collaborate in the interpretation of HbA1c values in type 1 diabetes mellitus.</td>
<td>HbA1c</td>
<td>It has been shown that BIISC represents feasible therapy and promoted the decrease in the daily dose of insulin, decrease in HbA1c values and decrease in the incidence of severe hypoglycemia.</td>
</tr>
<tr>
<td>A5</td>
<td>To compare continuous subcutaneous insulin administration through the Intermittent Subcutaneous Insulin Pump (BIISC) with other Multiple Insulin Dosage (MDI) regimens to reduce severe hypoglycaemia in patients with DM1.</td>
<td>HbA1c</td>
<td>It has been shown that BIISC represents feasible therapy and promoted the decrease in the daily dose of insulin, decrease in HbA1c values and decrease in the incidence of severe hypoglycemia.</td>
</tr>
</tbody>
</table>

By reading Figure 4, it was observed that, in four articles (80%), the method of glycemic monitoring was the HbA1c analysis. One (20%) article used the combination of CG and CGMS.

**DISCUSSION**

After presenting the general aspects of the research, we tried to answer their questions. In order to do so, three thematic categories emerged: “prospects for studies on DM1 in adolescents in Brazil”, “monitoring of glycemia in Brazilian adolescents with DM1: concepts and methods” and “the role of primary measurement techniques for DM1 control in adolescents”.

→ **Prospects for studies on adolescents with DM1 in Brazil**

From the reading of Figure 1, the wide time space between the publications of the articles: A1, in the year 2012; A2, A3 and A4 in 2008 and A5 in 2007. This aspect allowed to reflect on the difficulties in conducting research on glycemic monitoring in adolescents with DM1 in the country.

The lack of data on research with young people with DM1 in low and middle income countries, as well as incompleteness of data, lack of methodological rigor and old data are described as obstacles in the study of the incidence and prevalence of the disease in this life cycle.3

In this perspective, it is even highlighted the exclusion of children and adolescents in experimental studies. Such exclusion has been responsible for the lack of clear evidence regarding the treatment of DM1 resulting in recommendations with low probability in clinical trials for these age groups. That is, the management of DM1 in children and...
adolescents results from clinical trials in adults.1,2

When analyzed on the level of evidence, the surveys from A1 to A4 were classified with level four because they have descriptive designs and A5 classified with level three because they contemplate a quasi-experimental design. The shortcomings of clinical and experimental studies allowed corroborating the problem of the exclusion of children and adolescents in experimental studies on DM1,1,2

The analysis of the limitations and biases of the studies made it possible to verify aspects regarding the need for rigor in the diagnosis of DM1 in adolescents, the knowledge of the flow of these in health care levels and methodological precision. Study A1, which aimed to evaluate the economic influence on the care of Brazilian adolescents with DM1, according to ADA1, presented as a limitation the absence of autoantibodies and C-peptide measurement of the participants, allowing the inclusion of other types of diabetes in the study.

Autoimmune markers include islet cell autoantibodies and autoantibodies to GAD (GAD65), insulin, tyrosine phosphatases IA-2, IA-2b and ZnT8. Type 1 diabetes is defined by the presence of one or more of these markers.16

Another limitation presented by study A1 and that was also observed in studies A4 and A5 was the inclusion of patients only from the secondary and tertiary care networks. The development of research on adolescents with DM1 at the primary care level could add knowledge about the forms of monitoring and glycemic values of adolescents with the disease accompanied at this level of complexity.

Article A2, which was developed to evaluate the impact of H5 time on glycemic control of type 1 diabetic patients under continuous glucose monitoring, had, as a limitation, the absence of glycemic excursion in the morning shift.

Gestational diabetes mellitus monitoring is essential at puberty due to the phenomena of Dawn4 and Somogyi.4 Dawning refers to the increased need for insulin and glucose concentrations at the end of the night. In contrast, Somogyi describes the rebound effect5 of morning hyperglycemia after the occurrence of nocturnal hypoglycemia. The knowledge of glycemic levels compatible with one of these phenomena directly interferes with the insulin therapy of the adolescent.

With respect to A5, there were selection biases generating a small number of patients analyzed and they served as control group.

Monitoring of glycemia in Brazilian adolescents with DM1: concepts and methods

Glycemic or metabolic control aims to reduce fasting glucose levels between 90 and 130 mg / dl and to sleep between 90 and 150 mg / dl and HbA1c below 7.5%.1 Due to the need to maintain glycemic levels according to surveillance is a fundamental strategy to achieve the desired glycemic goals.

Blood glucose tests can be performed in the laboratory and / or at home, using porFigure devices, and reflect current and instantaneous blood glucose levels at the exact moment they are used.2 It is important to note that the use of porFigure devices has scientific data insufficient to recommend its use in the diagnosis of diabetes or of glycemic screening of the population.17

By observing the studies that made up this integrative research, we verified greater use of glycemic monitoring by laboratory analysis of HbA1c - studies A1, A3, A4 and A5. HbA1c reflects a history of glycemia over four months (120 days), and the research needs to monitor long-term glycemic levels.2

The term HbA1 represents a minor component of hemoglobin that has been modified by the enzymatic action of glucose. Among the various terminologies (glycated hemoglobin, glycohemoglobin, glycosylated and “glycosylated” hemoglobin), the latter is not indicated by ADA. Since the need for standardization, since 2011, the term glycohemoglobin (GHb) has been used for all forms of glycated hemoglobin (HbA1a, HbA1b and HbA1c).17

Dosing of HbA1c can be performed by several methods, however, high performance liquid chromatography (HPLC) is considered the ideal standard. Recently, the world standardization of HbA1c results was in progress and some Brazilian laboratories participated in the research. It is recommended that this test be performed three to four times a year in patients with DM1 and that the goal of values is less than 7.5% for the entire pediatric (including adolescents).2

GC consists of the insertion of a drop of capillary blood into disposable biosensing tape with glucose dehydrogenase or glucose content coupled to a medical device, the glucometer. Most of these devices use plasma glucose for quantification. Measurement values range from 10 to 600 mg / dl
depending on the manufacturer. However, it has, as a limitation of use, the obtaining of blood by the digital pulp, a process that is related to pain.²

It is noteworthy that glycemic monitoring mediated by HbA1c and GC may reveal discrepancies between the results obtained due to changes in metabolic control independent of glycemia such as: diagnosis of anemia and hemoglobinopathies, uremia, use of substances such as Acetyl Salicylic Acid) and presence of dyslipidemias. In addition, CG does not allow the verification of trends of glycemic profiles as in CGMS.²

CGMS can be performed by implanting a sensor in the patient's subcutaneous tissue that transforms the glucose into electronic signal directly proportional to the glucose concentration. The data are stored in the device and later transmitted by cable to computer software, which will allow the visualization of the glycemic excursions by means of graphs, facilitating the understanding of the glycemic profile. The sensors can be changed between three to six days depending on the manufacturer's recommendation.²

It is important to associate the level of recommendation of this method with lower HbA1 levels in adolescents. In article A2, the use of CGMS performed more glycemic measurements than CG favoring the metabolic control of adolescents who used it.

The guidelines and recommendations for laboratory analysis in the diagnosis and management of diabetes mellitus pointed out that although this evidence is not strong, real-time glycemic analysis may help adolescents in glycemic control.¹⁷

♦ The role of primary measurement techniques for DM1 control in adolescents

AMG (SMBG) is recommended for all DM1-treated patients by minimizing microvascular complications and detecting asymptomatic hypoglycemia by preventing episodes of severe hypoglycemia. It should be performed concomitantly with regular laboratory glycemia analyzes, contributing to the evaluation of the patients' performance in their glycemic excursions, as well as to the identification of interference in the analysis of porFigure devices resulting from changes in hematocrit, hypotension, hypoxemia, altitude change, humidity and ambient temperature.¹⁷

There are different consensuses for its frequency of use. The Guidelines and recommendations for laboratory analysis in the diagnosis and management of diabetes mellitus guides the AMGC to be performed three times a day. In Brazil, the Guidelines of the Brazilian Society of Diabetes (BSD) recommend that patients using MDI or CGMS perform CAGG at least four times a day.²⁻¹⁷

In the A3 and A4 studies, AMGC, via GC, was useful as a complementary method of CGMS¹³ and HbA1c, respectively. The association with the CGMS allows the calibration of this apparatus by inserting the GC values in it for the calibration. Otherwise, the association with HbA1c promotes the knowledge of oscillatory glycemia states favoring rapid interventions.²

Adherence of DM1 to AMGC directly affects its metabolic control. In a study in which adolescents had poor metabolic control, the intervention of a nurse, based on the supervision of glycemic monitoring and insulin application against the hyperglycemic states, was responsible for the reduction of 1.6% of the HbA1c of the same ones.¹⁸

In this context, the importance of AMGC supervision by parents / guardians and by health professionals who accompany adolescents, as adolescence is a transition phase¹⁶⁻¹⁹ between childhood, which requires supervision, and adulthood, which requires autonomy.

The use of the various methods of glycemic monitoring by adolescents with DM1 is complex, since it requires the availability of the necessary equipment and materials by the health services and / or their parents and guardians, training of the multiprofessional team that carries out the follow-up, promote their self-care and training of parents and guardians to supervise their children regarding the use and frequency of the method used.

The AMGC, although used in only one of the studies,¹² represents an important strategy for controlling the metabolic levels of adolescents with diabetes. Frequent monitoring allows the identification of hyper / hypoglycemic states favoring the rapid correction of glycemia through the application of insulin.

The use of the correct AMGC technique, as well as its adherence, can be encouraged through diabetes education, which is an area of knowledge in which techniques and themes are apprehended for adolescents to manage their disease.

Although there is still no consensus on diabetes education worldwide, institutions such as the Brazilian Society of Diabetes and results of research on the subject can guide this practice in the health services that provide care to this public.
CGMS is an important complementary method in the monitoring of the glycemia of adolescents with DM1, since, besides allowing the analysis of the glycemic variations, it can favor the adhesion of the monitoring. However, this technology is not widely used in the country due to its availability in the Brazilian market.1

In addition to the difficulties encountered by adolescents for glycemic self-monitoring, the results for carbohydrate counting, interpretation of results and insulinization0-1 that make them potential targets for micro and macrovascular complications of diabetes in the long term.

**CONCLUSION**

The researches and analyzes carried out allowed the knowledge of the glycemic monitoring methods used by Brazilian adolescents with DM1 reaching the main objective of this study. They were: CG, CGMS and laboratory analysis of HbA1c, the latter being the most used method.

The analysis of the articles also allowed to verify that there are knowledge gaps regarding the thematic of adolescents with DM1 followed in the level of primary attention. Future research that addresses this level may elucidate issues of accessibility to health services, describe referral flow and counter-referral for secondary and tertiary care, and identify failures in therapeutic follow-up, as well as identify adolescents at high risk and presence of disease complications in the primary level.

It is understood that there is a clear difficulty, by the researchers, to include young people with diabetes in the studies of randomized and experimental clinical trials. This phenomenon may be associated with difficult metabolic control at this stage, as a result of hormonal and behavioral changes, as well as the need for parents' authorization to participate in researches with such designs.

It is recommended that research be developed with this public through a multidisciplinary and intersectoral perspective contemplating contents with methodological rigor important for the area of diabetology and involving their parents / relatives.

**REFERENCES**


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