

Adolescent's Experiences with Diabetes Self-Management and the Use of Carbohydrate Counting in Their Everyday Life with Type 1 Diabetes

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Aim: The aim of this study was to describe adolescents' experiences with diabetes self-management and the use of carbohydrate counting as a tool for calculating insulin doses in everyday life with type 1 diabetes.

Methods: We used a qualitative study design. Individual interviews were conducted with 14 adolescents (seven boys and seven girls, aged 16–18 years) with type 1 diabetes by using a semi-structured interview guide. We used purposive sampling, recruiting the participants from one paediatric outpatient clinic in Norway. Thematic analysis was used for the data analysis.

Findings: We identified two main themes, each comprising three subthemes: (1) "Diabetes treatment is difficult but can be well adapted" with subthemes "Diabetes influences my entire life, with a lot of fuss and takes time", "Having diabetes turned out to be manageable", and "Need some help and support, but not too much"; (2) "Carbohydrate counting is useful but often not used" with subthemes "One counts the carbs, then the pump calculates the insulin doses", "Carbohydrate counting gives better blood glucose, but I do not always bother to use it", and "After a while, one just uses one's own experience."

Conclusion: The study showed that adolescents with type 1 diabetes experienced that the diabetes treatment influenced their entire life in a substantial manner. Nevertheless, the demands of the disease and the treatment tasks were perceived very differently. Some articulated that carbohydrate counting was appreciated as a suitable tool for dosing insulin and optimizing glycaemic control. Others did not use carbohydrate counting at all and described to use their own experience. The findings support the importance of individualizing diabetes follow-up and adapt the training in treatment tools to everyone's situation and preferences.

Keywords: carbohydrate counting, adolescents, interviews, qualitative approach, self-management, type 1 diabetes

Introduction

Type 1 diabetes (T1D) is a chronic insulin deficiency disease in which insulin-producing cells in the pancreas are destroyed, leading to insulin deficiency.¹ In T1D, insulin treatment is vital for regulating the body's glucose levels, and well-adapted insulin treatment can contribute to near-normal levels.^{1,2} However, insulin treatment is complicated because the need for insulin varies from day to day in the same individual and is affected by what people eat, activity, hormonal conditions, and other conditions. Insulin treatment is especially demanding in adolescence when several hormonal, cognitive, and social changes occur simultaneously.³

Adaption between insulin doses and food intake is key in the treatment of T1D. The carbohydrate content is the main factor that affects the need for insulin in connection with meals. Thus, it is important that mealtime insulin doses are adjusted according to carbohydrate intake.⁴ Carbohydrate counting is commonly used to adapt insulin doses to carbohydrate intake. The method can be used in different ways. However, there is no agreement on how the method

can best be used for children and adolescents, and knowledge of how children and adolescents use carbohydrate counting in their everyday life is limited.

Background

Diabetes treatment involves significant and complex self-management tasks to keep blood glucose at a satisfactory level.⁵ It is estimated that people with diabetes perform 95% of their diabetes treatment and care themselves. Self-management of T1D involves dosing and administering insulin, monitoring glucose levels throughout the day, and maintaining an adapted diet and physical activity levels.⁵ The complex considerations required might explain why many adolescents with T1D do not achieve the recommended treatment goal for blood glucose regulation measured by glycosylated haemoglobin A1c (HbA1c).⁶ Data from the Norwegian Childhood Diabetes Registry (NCDR) show that only 36% of children and adolescents with T1D achieve treatment goals for blood glucose with HbA1c <53 mmol/mol.⁷ Because high blood glucose level over time is the biggest risk factor for developing diabetes-related micro- and macrovascular complications in people with diabetes, optimization of blood glucose levels is the most important aspect of diabetes treatment.⁸

Nutrition is essential in the treatment of T1D. In the large and important Diabetes Control and Complication Trial (DCCT) conducted from 1983 to 1993, dieticians implemented various nutritional methods to help patients achieve satisfactory blood glucose regulation. One of the four meal planning methods used in the study was carbohydrate counting.⁹ In recent years, carbohydrate counting has undergone a new renaissance, and now forms an essential part of the training for self-management of T1D. The purpose of carbohydrate counting is to adapt mealtime insulin doses to the intake of carbohydrates and subsequently improve blood glucose regulation. Studies have shown that carbohydrate counting can provide a better quality of life for children and adolescents with T1D.¹⁰ The method can provide flexibility around meals, and the management of the disease can be more easily adapted to the desired lifestyle.^{10,11} Some studies have also shown that carbohydrate counting can have a positive effect on HbA1c and provide better blood glucose regulation, but the results vary between studies and more research is needed.^{10,12–14} However, inaccurate carbohydrate counting is common and associated with higher daily blood glucose variability.¹⁵ The varying results within this research field indicate a need for more research and knowledge about how people with T1D use carbohydrate counting in their everyday life. After a systematic literature search, we have not been able to identify qualitative studies that deal with adolescents' experiences with carbohydrate counting. Thus, knowledge on how adolescents use carbohydrate counting in their everyday lives is limited.

Aim

The aim of this study was to describe adolescents' experiences of diabetes self-management and the use of carbohydrate counting as a tool for calculating insulin doses in their everyday life with T1D.

Patients and Methods

Design, Setting and Recruitment

The study had a qualitative study design. A qualitative approach is suitable for studies that aim to gain knowledge about people's experience of their situation.¹⁶ We collected the data through individual interviews. To obtain data from individuals who represent the group of particular interest and relevance to our research question, we used purposive sampling to recruit participants.¹⁶ Adolescents aged 16–18 years with T1D for at least 1 year were invited to take part in the study. As qualitative interviews are used when the researcher wish to gain an understanding of participants views and experience of specific aspects of the treatment, adolescents using various types of insulin regimen (insulin pump or a multi-injection regime with insulin pens) with various levels of glucose regulation, were invited to take part in the study.

The diabetes nurse at one paediatric outpatient clinic in Norway contacted eligible adolescents by phone to give verbal information about the study. Thereafter, written information and a consent letter were sent by regular mail to those who were interested in participation. When the adolescents returned a signed consent form in pre-stamped envelopes,

they were contacted by the first author. Fourteen adolescents between 16 and 18 years of age gave written consent (seven girls and seven boys). All participants used a continuous glucose monitoring (CGM) system. Six used insulin pens and eight used an insulin pump for insulin administration.

Data Collection

Based on the research question, an interview guide was developed by the research team (AU, AH, MG) and one representative health service user gave valuable input to improve the guide. The main topics and follow-up topics in the interview guide are listed in Table 1. The questions focused on the participants' experiences of living with diabetes, diabetes self-management, insulin dosing, and the adolescents' experiences with carbohydrate counting in their everyday life. The interviews started with a broad opening question about the adolescent's diabetes care to make the adolescents familiar with the interview situation. Then the main topics and follow-up topics in the interview guide were asked to further elaborate on the topics. Although the situations will determine what appropriate probes that are needed to use during interviews, some questions were prepared in advance. Examples of probing questions were "What do you mean?", "Tell more about that" or "Can you describe this more in detail?". A pilot interview was conducted with the health service user representative who was recruited from the hospital's youth council. The pilot interview resulted in some adjustments to the interview guide and was not included in the analyses. All the interviews were conducted as telephone interviews. The adolescents decided when the interview should take place, and the interviews lasted between 14 and 39 minutes; the average was 25 minutes. All interviews were audiotaped and transcribed verbatim.

Data Analysis

The analysis followed the six steps of thematic analysis described by Braun and Clarke.¹⁷ The six steps are: 1) familiarizing with data, 2) generating initial codes, 3) searching for themes, 4) reviewing themes, 5) defining and naming themes, and 6) producing report.

Initially, all researchers (AU, AH, MG) read and reread the transcribed data several times to become familiar with the data. The researchers were all female registered nurses with extensive knowledge of diabetes. AU and AH have first-hand

Table 1 Topics in the Interview Guide

Aim: To describe adolescents' experiences with diabetes self-management and the use of carbohydrate counting as a tool for calculating insulin doses in everyday life with type 1 diabetes.	
Main Topics	Follow-Up Topics
1. Can you please tell me about your experiences of living with diabetes and diabetes treatment in your everyday life?	<ol style="list-style-type: none"> 1. Can you please tell me about yourself and your diabetes? 2. Can you please describe how you experience diabetes management in your everyday life? 3. Is there anyone who helps you with your diabetes management? 4. How do you experience the education you have received related to diabetes self-management? 5. Are you happy with how you manage your blood glucose control? 6. Can you please tell me about your experience with insulin dosing?
2. The experiences of carbohydrate counting as a tool for insulin dosing	<ol style="list-style-type: none"> 1. When and how did you receive education in carbohydrate counting? 2. Can you please tell me how and when you use carbohydrate counting in your everyday life? 3. What do you think about the method? 4. Do you think carbohydrate counting is a valuable tool for you? 5. Do you think carbohydrate counting is easy to use in your everyday life? 5. Do you think that carbohydrate counting helps you to better insulin dosing and better blood glucose regulation?

knowledge of providing diabetes care as diabetes nurse specialists within specialist health care services; MG and AH have extensive experience in diabetes research and in conducting qualitative research studies. AH also has many years of lived experience with T1D. The data were coded by each author individually and then further organized based on a list of different codes that were identified in the data material. Thereafter, the researchers met for a workshop to sort the codes into a range of possible aspects and patterns and discuss how different codes could be combined to form more overarching themes. Data that fell out of the scope of the previous coding step became new codes and new themes were created. The themes were reviewed and renewed in step four. The project group defined and delimited the final themes and agreed on the essence of the themes. In this step, it was important to be able to clearly define the themes and define suitable names.

Ethics

The adolescents were informed that participation was voluntary and that they could withdraw from the study at any time. All participants gave written consent. Consent from parents was not necessary because the children were above 16 years of age, and the research did not include any physical intervention or drug testing. The informed consent included information about publication of anonymized responses. None of the researchers had any relationship with the adolescents in the study. The data material collected was anonymized in accordance with ethical guidelines. The study was conducted in accordance with the Declaration of Helsinki. An application was sent to the Regional Ethics Committee for Human Research (REK), which assessed the project as not requiring notification. The project was approved by the Data Protection Officer at the Hospital Innlandet and the Norwegian Centre for research Data (NSD) (NSD ref. 698544).

Findings

We identified two main themes regarding how adolescents with T1D experienced to self-manage their diabetes and how they used and experienced carbohydrate counting as a tool for insulin dosing: “Diabetes treatment is difficult but can be well adapted”, and “Carbohydrate counting is useful but often not used”. Under each theme, we identified three subthemes as shown in [Table 2](#).

Diabetes Treatment is Difficult but Can Be Well Adapted

The experiences that were described by the participants under this theme are reflected through the three subthemes: “Diabetes influences my entire life, with a lot of fuss and takes time”, “Having diabetes has become part of me” and “Need some help and support, but not too much”.

Diabetes Influences My Entire Life, with a Lot of Fuss and Takes Time

The interviews indicated that some adolescents found diabetes very difficult to cope with, that it was demanding and that it took too much time. It was something they had to think about all the time and that influenced their entire life in a way. Thoughts related to having diabetes throughout life could knock them out. It gave them a feeling of injustice and anger, and they questioned why exactly they got diabetes. One said:

Table 2 Themes and Subthemes

Theme	Subtheme
1. Diabetes treatment is difficult but can be well adapted	<ol style="list-style-type: none"> 1. Diabetes influences my entire life, with a lot of fuss and takes time 2. Having diabetes turned out to be manageable 3. Need some help and support, but not too much
2. Carbohydrate counting is useful but often not used	<ol style="list-style-type: none"> 1. One counts the carbs, then the pump calculates the insulin doses 2. Carbohydrate counting gives better blood glucose, but I do not always bother to use it 3. After a while, one just uses one's own experience

I wish I did not get it at all. Because it affects my whole life in a way. (D9)

Experiences of chaos and stress were described in relation to the large number of treatment tasks the adolescents had to keep in mind every day. It was described as stressful to always check glucose level and perform all the demanding tasks they just had to do with no choice. In a way they felt trapped, and one said:

It's almost all the time. I have to think about what my blood glucose is; if it's high or if it's low, and I have to take insulin before I eat, so it takes a lot of my time. (D1)

A lot of hassle and stress was described in relation to the routine replacement of the technical equipment of the insulin pump and CGM system that they needed to do several times a week. Although they experienced that there always was a lot to keep in mind, things went well overall. They changed the equipment themselves and did not need help, even though reminders from parents were described as valuable. One said:

Ehm... in most cases it goes pretty well, but sometimes it's challenging with a lot of effort needed. But then you establish a good routine. However, there is often stress with replacement of Dexcom and pod, or other equipment, and when you sometimes are busy and forget it in a way ... But overall, it goes pretty well. (D3)

Having Diabetes Turned Out to Be Manageable

Other adolescents described the opposite experience of having diabetes. It was tolerable, in a way, and had turned out to be manageable. They did not experience that they spent much time on their diabetes despite all the daily treatment tasks. The time they spent was mainly related to glucose measurements and insulin administration. However, some said that they constantly took a quick look at the CGM just to get an insight into the glucose level, but with no stress associated with that. It emerged that having diabetes was more difficult and challenging in the beginning, but things improved as time went on. One said:

The diabetes does not really take too much of my time, mostly only when I take my insulin and when I use the Dexcom app. For example, if I am on Snapchat, I kind of go to the Dexcom app as well, just to check my blood glucose. It kind of just becomes a part of me. The Dexcom app is a tab I always have open. (D4)

Even though some participants described that they were tired of having diabetes and that now and then there was a lot of chaos, although having diabetes could also be experienced as a well-adapted routine. Having diabetes had just become a habit. Some adolescents had established proper routines to check their glucose level and take insulin based on what they were going to eat and what they were going to do without involving a lot of emotion in relation to these practical tasks. They felt that they could live their life like people without diabetes, given that they gave attention to glucose levels, food and insulin administration. One said:

...but I really think that if I did not have diabetes, I would be living my life in the same way, except that I now must look after my blood glucose. (D10)

Need Some Help and Support, but Not Too Much

The interviews revealed that adolescents appreciated advice and guidance from their parents. The parents gave reminders and tips and advice on insulin dosing. In addition, some helped with carbohydrate counting at meals. If insulin doses were forgotten, the parents were there to remind them. Some parents also helped with insulin dosage and delayed insulin doses in relation to rarely eaten food or snacks. One said:

I take care of most of the tasks myself, but if I am at home with mum and dad and we eat pizza for example, which contains a lot of wheat flour with a lot of carbohydrates involved, they remind me to take extra insulin and things like that... (D6)

The participants had positive attitudes to receiving help from parents, as long as it was not too much. Help from parents could quickly become a nuisance; they sometimes felt that they did not want the parents to interfere. They described

a desire to be independent without a need for help. However, if they needed help, they experienced having people around that can help them. One said:

No I am not dependent on them for the regulation of my blood glucose. I do it myself. But..., yes..., no it is really just me. I do not need help. It's not that I lack possibilities for help. (D3)

Some adolescents appreciated that the parents used the following function in Dexcom to follow the glucose values continuously. They felt secure when their parents could follow their glucose level, especially at night. Others thought it was negative that their parents monitored their glucose; it gave them a feeling of being under control of parents. One described turning off parents' ability to follow because it became too fussy, and one said:

I have stopped sharing with them after I received messages with reminders that I have to take insulin and check my blood glucose and blah blah. (D9)

So, although some help from parents was appreciated, an overall need to be independent and have control themselves emerged through the interviews.

Carbohydrate Counting is Useful but Often Not Used

We identified three subthemes under this theme: "One counts the carbs, then the pump calculates the insulin doses", "Carbohydrate counting gives better blood glucose, but I do not always bother to use it" and "After a while, one just uses one's own experience."

One Count the Carbs, Then the Insulin Pump Calculates the Insulin Doses

The adolescents who treated their T1D with an insulin pump with bolus calculator described that they calculated the amount of carbohydrates they planned to eat and put the number of grams of carbohydrates into the insulin pump. Then, the pump suggests the insulin dose. Some adolescent experienced that the insulin pump did most of the work for them. One said:

I feel that the insulin pump does a lot of the work for me with insulin dosage. I calculate the carbohydrates. (D4)

Those who did not use an insulin pump said an app that showed pictures of different foods with their carbohydrate content was useful. They also described a useful booklet with similar pictures of food's carbohydrate content. When they were unsure of the amount of carbohydrates in a meal, they could use either the app or the booklet. Both the app and the booklet were described as appropriate aids.

Carbohydrate Counting Gives Better Blood Glucose, but I Do Not Always Bother to Use It

The use of carbohydrate counting was experienced as having a positive influence on blood glucose. The adolescents had learned how many grams of carbohydrates 1 unit of insulin can handle and actively used carbohydrate counting. They described being happy with the method and experiencing mastery when they count carbohydrates. The method was perceived as simple and useful for blood glucose regulation. One said:

If I count carbs and take the right amount of insulin, it helps my blood glucose a lot. (D10)

The interviews revealed various ways of using carbohydrate counting. Some did not use the method regularly although it was experienced as helpful. Some said that they had never learned the method properly, and some did not use it because they found it boring to have diabetes and count carbohydrates. Others described it as a chore to try to find the content of carbohydrates in certain foods and therefore they did not bother to use the method. Instead, they guessed how much carbohydrate was in the food. Others said that they only knew from experience how many carbohydrates there were without counting. They did not follow carbohydrate counting slavishly but may have used it at certain meals. One said:

I do not use carbohydrate counting for absolutely all meals because I do not bother to find out exactly what each food contains. I don't bother to find out what certain foods contain. (D4)

After a While, One Just Uses One's Own Experience

It emerged from the interviews that the adolescents often used their own experience when dosing insulin for food. They had learned how much carbohydrate the food contained. They described using their eyes to know how much insulin their body needs. They glanced over the dinner plate and knew approximately how many carbs there were. More exact counting of carbohydrates in the beginning and rough estimation later were described. One said:

I look at what I have on the plate that affects the blood glucose. If we eat pasta, potato or salad, then I know that there are a lot more carbohydrates, for example, in pasta and then I take more insulin. If I eat salad, I count based on what I eat, but yes, what can I say, it's pretty automatic. (D8)

Some participants said that they had moved away from carbohydrate counting because after a while they had learned a lot about the carbohydrate content of the foods they eat. With frequently eaten foods, they had simply learned how much insulin they need because past experience had gone well, and they ended up with good glucose levels. However, it emerged from the interviews that the adolescents perceived it was important to learn how to count carbohydrates, but eventually they did a rough calculation based on experience, and it became automatic. One said:

I think it's important to learn the method, but eventually you just calculate it approximately in your head. I do not count as much as before. (D6)

Discussion

The main finding of this study was that adolescents experienced having T1D and keeping up with diabetes treatment very differently. Some adolescents said that they had become acquainted with having diabetes, and it had turned out to be quite manageable given that they gave sufficient attention to glucose levels, food and insulin administration on a routine basis. Others had a lot of resistance to take on the required responsibility and described having diabetes as rather stressful. They felt trapped in a way, with demanding tasks to maintain, such as always checking glucose levels, and keep up with all the time-consuming tasks they just had to do with no choice. It put them into a somewhat chaotic situation, and the diabetes treatment was experienced as difficult to cope with. It occupied too much time and energy in everyday life.

Consequently, the adolescents in this study solved the treatment challenges in a very different way. Some used carbohydrate counting consistently to dose insulin before meals while others did not use the method at all and expressed this openly. The latter explained that they dosed insulin based on experience without any calculations. The findings shed light on how the adolescents experienced and solved treatment challenges and highlight the need for putting even more emphasis on individualizing and differentiating diabetes follow-up in paediatric outpatient clinics. Research has shown it as a considerable problem that many adolescents with T1D are unable to achieve satisfactory blood glucose regulation due to psychological problems.^{18,19} Accordingly, some adolescents in our study expressed that having T1D was hardly manageable. Others coped well with the treatment tasks and demands and expressed that they primarily needed a follow-up related to technological and medical concerns. They expressed clearly that the treatment did not involve their life emotionally because they only did what they were supposed to do to keep their glucose levels as best as possible within the normal range.

The various needs and challenges described by the adolescents may indicate that health care professionals should develop more targeted follow-up to adjust consultations and training to dose insulin in a more constructive way to reach different personalities, temperaments, behaviours, and life situations. Then, all adolescents, independent of their confidence to self-manage the disease, can get the kind of support that they need to manage emotional as well as medical challenges related to the disease. Also, previous research has demonstrated the importance of individualizing diabetes education to everyone's needs.²⁰ It is important that adolescents with emotional challenges are maintained by a team of professionals with sufficient knowledge and skills to also meet the psychological needs that are expressed in consultations.

A supportive parenting relationship can have a positive impact on the psychological well-being and health of the adolescents.²¹ Nevertheless, the adolescents in our study vary noticeably in how they express their need for help from

parents and friends, dependent on their level of maturity as well as communication patterns in the family. Some adolescents expressed clearly that they needed some help and support, but not too much. Self-management of T1D is important for psychological well-being and satisfactory glucose control. If self-management is experienced as difficult and overwhelming, it could have a negative effect on glucose regulation.⁵ In line with the experiences of some of the adolescents in our study, a study by Carroll and Marrero²² showed that some adolescents experienced their parents as being condescending and controlling. Therefore, they did not want their parents to be involved in their diabetes treatment. However, several adolescents in our study said that their parents acted as reminders when it came to checking glucose and taking insulin. It is conceivable that health professionals can help parents and adolescents to clarify the division of responsibilities and roles related to the diabetes treatment to a greater extent. In addition, professionals should give advice and follow-up adapted to the individual family.²³

The adolescents used carbohydrate counting to varying degrees. Previous studies have shown that using carbohydrate assessment can improve blood glucose control and reduce HbA1c.^{10,12} In our study, some adolescents realized the benefits of carbohydrate counting and used the method with no resistance. The method worked well, and they used it willingly to maintain good glycaemic control. Others perceived carbohydrate counting as a useful tool, but they did not use the method. A study by Spiegel et al²⁴ showed that adolescents with T1D were not accurate in counting carbohydrates and often over- or underestimated the number of grams of carbohydrates in a meal. It is conceivable that the adolescents in our study who said they did not use carbohydrate counting thought it was too complicated to use numbers and calculations to dose insulin. They said that they used their own experience to dose insulin and felt that they succeeded with it. It is reasonable to question whether the adolescents were as good at calculations to dose insulin as they perceived themselves. Younger people might not be conscious enough to utilize their own experience in a way that leads to better glucose regulation. Data from the NCDR has shown that only 36% of children and adolescents achieve treatment goals and have HbA1c <53 mmol/mol.⁷ Thus, to meet the adolescents' needs in everyday life, diabetes nurses and other health care professionals should be more focused on discussions related to glucose regulation and how they can switch between counting carbohydrates mathematically and a more experienced-based calculation as time goes on.

Strengths and Limitations

The study has strengths and limitations. In a qualitative study, trustworthiness is created by four criteria: credibility, dependability, confirmability, and transferability.²⁵ The research team had experience and extensive knowledge of both clinical treatment of adolescents with diabetes and qualitative study methodology. This strengthens the study's credibility. A pre-understanding of the phenomenon under study can be both a strength and a limitation. On the one hand, it can help researchers to collect rich and sufficient data, construct a relevant interview guide and ask adequate follow-up questions during the interviews. On the other hand, the analysis can be affected by the researchers' own experiences of having diabetes or being a diabetes nurse specialist. To avoid the latter and to strengthen dependability, a reflective open-minded discussion of the data took place among the researchers during the analysis. Through a well-described design, including strategic selection of adolescents aiming to reach a rich variety of perceptions, confirmability was maintained. However, it is conceivable that the adolescents consciously or unconsciously might report either positive or negative perceptions of carbohydrate counting. Such a bias can threaten the study's validity and trustworthiness.¹⁶ However, the interviewer, a diabetes nurse, used a pilot-tested interview guide with probing questions with the aim of elaborating the full meaning of the perceptions described by the adolescents. Also, the use of the SRQR checklist for reporting qualitative research strengthen the study's validity.²⁶

Conclusion

This study showed that adolescents with T1D experienced that the diabetes treatment influenced their entire life in a substantial manner. Nevertheless, the demands of the disease and the treatment tasks that they had to keep up with were perceived very differently. Some articulated that carbohydrate counting was appreciated as a suitable tool for dosing insulin and optimizing glycaemic control. Others did not use carbohydrate counting at all and described to use their own experience. The findings support the importance of individualizing diabetes follow-up and adapt the training in treatment tools to everyone's situation and preferences.

Acknowledgments

We thank all the adolescents who participated in the study. We also thank the diabetes nurses at Hospital Innlandet, Elverum, who identified and contacted the participants initially.

Author Contributions

All authors made a significant contribution to the work reported and contributed to the conception, study design, execution, analysis and interpretation. AU conducted the interviews. Further, all authors took part in drafting, revising and critically reviewing the article, and all gave final approval of the version to be published. All authors have agreed on the journal to which the article has been submitted and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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