Estimating the utility value of hypoglycaemia according to severity and frequency using the visual analogue scale (VAS) and time trade-off (TTO) survey

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Abstract

Objectives The primary objective of this study was to estimate the health utility values for hypoglycaemia events according to their severity and frequency. The secondary objective was to compare the health utilities between those with Type 2 Diabetes Mellitus and the general population.

Method The health utilities of hypoglycaemia event were measured using Visual Analogue Scale (VAS) and Time Trade-Off (TTO) methods among conveniently sampled consenting adults (>18 years and literate in either English or Malay language), which were then divided into two groups: those in the general population (GP) and those with Type 2 Diabetes Mellitus (T2DM). Each respondent was required to value 13 different health states, including frequencies of daytime hypoglycaemia and nocturnal hypoglycaemia, each depending on its severity (non-severe or severe).

Results 256 respondents from the GP and 99 respondents with T2DM completed the survey. The T2DM group gave higher VAS-values compared to the GP group. The highest mean VAS-utility value for non-severe nocturnal hypoglycaemia occurring once monthly was 0.543 (SD 0.161), and for severe daytime hypoglycaemia occurring once quarterly was 0.293 (SD 0.162) which was the lowest utility value compared to other health states. However, non-severe nocturnal hypoglycaemia occurring once quarterly was 0.537 (SD 0.284) and has the highest TTO-utility value. Severe nocturnal hypoglycaemia occurring once quarterly has the lowest utility value which was −0.104 (SD 0.380). Daytime hypoglycaemia has lower utility value compared to nocturnal hypoglycaemia. Severe hypoglycaemia has a greater disutility compared with the non-severe hypoglycaemia in both studied groups.

Conclusion The findings show that as a health utility, hypoglycaemia has a substantial impact on utility with severe hypoglycaemia having a greater negative impact compared to non-severe events across the board. This highlights the importance of preventing development of severe hypoglycaemia in patients with Type 2 Diabetes Mellitus at any time of the day.

Keywords Hypoglycaemia · Utility value · Time trade-off · Visual analogue scale

Introduction

Diabetes Mellitus (DM) is a metabolic disease characterized by hyperglycaemia resulting from defects in insulin secretion (1). Hypoglycaemia is a detrimental complication that arises during uncontrolled diabetes treatment and requires prompt

recognition and treatment in order to avoid extreme morbidities such as chronic organ and brain damage (2). Patients with hypoglycaemia have nearly twice the mortality rate compared to those without the complication (5). Generally associated with lower Health-Related Quality of Life (HRQoL) and depression, hypoglycaemia reduces satisfaction with diabetes treatment, which in turn could reduce adherence to treatment (3). The risk of hypoglycaemia is higher among patients with strict glucose control, especially those receiving treatment with insulin secretagogues such as insulin, Gliclazide, and Repaglinide (4).

Utility is an economic method to quantify HRQoL and is commonly applied in Cost-Utility Analysis (CUA) for evaluating the economic value in treating diabetes. Hypoglycaemia's health utility can be obtained by directly eliciting preferences using a Visual Analogue Scale (VAS) and

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Time-Trade Off (TTO). In VAS, respondents give a rating based on their preference on a scale (7). VAS is, however, generally considered to be inferior to TTO due to its non-choice task and scaling biases (8). The TTO method, on the other hand, elicits preferences for health states by making the respondents imagine living a defined number of years in an imperfect health state (9). In this method, the respondents hypothetically trade their life expectancies for imaginary health states with a progressive line (9). Therefore, ignoring the utility implication of hypoglycaemia would result in an erroneous conclusion regarding the overall impact of a diabetes treatment (6).

Although there are studies describing the utility value of diabetes-related hypoglycaemia events (10, 11), exploring the relative utilities for the Malaysian population is critical because the health utility value is sensitive and may be affected by cultural norms and the availability of medical technology (12). For instance, even though certain countries have similar cultures and languages, the disutility of hypoglycaemia events is different in Canada, the United Kingdom, and the United States (10). With insulin ranking in as, the third most commonly used agent employed to treat Type 2 Diabetes Mellitus (T2DM) at the Malaysian Ministry of Health's facilities (13), a local preference in relative utility values with regard to hypoglycaemia is required as it is an important value for CUA, especially in evaluating intensive insulin treatment known to induce hypoglycaemia.

The primary objective of this study is to estimate the utility values for hypoglycaemia events using the VAS and TTO methods. These utility values can be applied as an input in diabetes decision models to estimate the Quality-Adjusted Life-Years (QALYs) (7). The secondary objective is to compare the utility values between T2DM patients versus the general population.

Methodology

Study design

A cross-sectional survey was carried out using face-to-face interviews on convenient samples in the state of Penang, Malaysia. All the consenting respondents had to be at least

18 years of age and able to read in either English or Malay language. Agreement was obtained from the respondents before the interviews proceeded.

In this study, the hypoglycaemia event is divided into two categories: minor and severe hypoglycaemia. The minor hypoglycaemia events in the interview is defined as the event that happened suddenly because of low blood sugar. The patient might feel shaky, dizzy, sweaty, or irritable. The patient might experience confusion or sick, get a headache, or feel heart pounding (have palpitations). In the interview, the interviewer told the respondent that these symptoms usually do not last long and will go away after eating or drinking something that contains sugar but it has the possibility that the patient might feel tired and not even remember what happened. A severe hypoglycaemia event was defined in this study as an event that happened suddenly because of very low blood sugar. The respondents are unable to treat it themselves; and will need help from another person, possibly medical assistance. A severe hypoglycaemia may occur after a brief period of feeling shaky, dizzy, sweaty, irritable, or confused. The respondents who experienced severe hypoglycaemia may experience seizures, convulsions, further confusion, fainting, or fall into a coma. In rare cases it is life-threatening. There were 12 characteristics of hypoglycaemia health states, each defined by different hypoglycaemia experiences (minor or severe) according to frequency episodes, severity, and the time of onset in addition to three anchor states which are perfect health (PH), well controlled diabetes either for diabetes patients (WD1) or non-diabetes patients (WD2), and death (DE) (Table 1). All the 12 hypoglycaemia health states were randomly assigned to 64 blocks that consisted of one non-severe daytime hypoglycaemia health state, one non-severe nocturnal hypoglycaemia health state, and one severe hypoglycaemia health state (either daytime or nocturnal). Each respondent was told to value one of the 64 blocks of health states to avoid fatigue.

Respondents were excluded from final data analysis based on the following criteria:

- A. Inconsistency: the health state of baseline diabetes (without a hypoglycaemia event) was valued below all three hypoglycaemia health states.

Table 1 Characteristics of hypoglycaemia health states based on frequency, severity and time of onset

Parameter	Frequency of Hypoglycaemic Episodes				
	Once annually	Once quarterly	Once monthly	Once weekly	Three times weekly
Baseline diabetes	Hypoglycaemic episodes = 0				
Non-severe daytime events		X	X	X	X
Non-severe nocturnal events		X	X	X	X
Severe daytime events	X	X			
Severe nocturnal event	X	X			

- B. All health states were valued as being equal to death.
- C. All health states were valued the same.

Instrument

The survey was administered by 25 interviewers consisting of pharmacy students. The interviewers were trained before the data collection process. The training consisted of a 5 h lecture covering the data collection process and mock interview session. This was followed by interview practice session with at least five respondents. Finally, the interviewers were assessed for their field competency by conducting the interview with their supervisors. An interviewer script was developed to standardize the interview sessions. Responses were recorded on the script and a self-completion booklet. The booklet contained batteries of questionnaire including the EQ-5D-5 L, EQ- VAS, a diabetes knowledge questionnaire, and demographic questions.

The respondents were first instructed to rate their health state on that particular day using EQ-5D-5 L and EQ- VAS. The VAS and TTO methods were used to value the hypoglycaemia health states. The VAS method uses a 20-cm thermometer-like vertical line (similar to the EQ- VAS) to rate four different health states with different levels of severity and frequency of hypoglycaemia events. In the TTO method, the respondents were presented with a set of instructions which required them to imagine themselves in a particular health state. They were given the same health states used with the VAS method.

TTO utility values were determined by posing two hypothetical questions. Firstly, the patients were asked to justify whether they would prefer to live in a particular health state with hypoglycaemia for 10 years, to be dead, or the particular health state worse than being dead. If the respondent was willing to live in the particular health state, they could choose between two options: (A) to live in full health for five years, or (B) to have the particular health state and live for 10 years. If the respondents chose option B, this indicated that the utility of this health state was more than 0.5. Conversely, their health state was less than 0.5 when the respondents chose option A, because this meant that they were willing to exchange their remaining years to avoid living with the particular health state. On the other hand, if the respondents preferred to die than live in their health state for 10 years, they were directed to another hypothetical situation where they had a total of 10 years of life consisting of a few years living in their health state and the remaining years in perfect health. The interviewers decreased the number of years of living in their health state and increased the number of years of perfect health until the respondents preferred to be alive than dead. The utility value was obtained by identifying the point of indifference by repeating the same

questions and changing only the number of years of living in full health each time.

The diabetes knowledge assessment questionnaire was adapted from Gracia et al. (2001) (14). It is a widely used tool (15, 16) containing 24 questions designed to assess overall diabetes knowledge (14). Each question has three possible answers: “Yes”, “No”, and “I don’t know”. The items were scored with one point given for a correct answer, and zero points given for an incorrect answer or “I don’t know” response.

Statistical analysis

All analysis was performed using the SPSS version 17.0 Statistical Software. The mean utility value was calculated for each health state using equations as below:

$$\begin{aligned} \text{VAS} &= \frac{X}{100}, \text{ the VAS is rescaled to value between 0 and 1} \\ \text{TTO (better than death)} &= \frac{X}{10}, \text{ utility value is between 0 and 1} \\ \text{TTO (worse than death)} &= -1 + \frac{X}{10}, \text{ utility value is between 0 and -1} \\ X &= \text{the value rated by the respondent} \end{aligned}$$

The disutility for the hypoglycaemia events was calculated by dividing the difference between the mean utility and the baseline diabetes state utility by the number of annual events. The association of the exclusion criteria was determined using chi-square and independent sample t-tests.

Ethical approval

The study was approved by the Ministry of Health Medical Research Ethics Committee (MREC). The registration ID for the study was NMRR-17-99-33,826.

Results

The recruited sample size for the general population (GP) was 256 respondents and 99 for respondents with Type 2 Diabetes Mellitus (T2DM). The respondents with Type 2 diabetes mellitus were received at least one hypoglycemic agent. A total of 140 respondents from GP and 77 respondents from T2DM completed the survey correctly and were included in the final analysis. The number and flow of the respondents for each studied are presented in Fig. 1. The majority of the respondents were Malay ($n = 188$, 73.4%) with no family history of T2DM ($n = 157$, 61.3%) in the general population. The respondents from the general population were younger compared to the diabetes group. The background information for each population is presented in Table 2.

Figure 2 shows the comparison of the different health states using mean VAS and TTO values respectively. The utility

Fig. 1 The number and flow of respondents for each studied group

value for well-controlled diabetes and diabetes with hypoglycaemia events was slightly higher for T2DM respondents compared to GP respondents for both approaches. In general, the severity of hypoglycaemia affected the utility values. Non-severe hypoglycaemia has a higher utility value compared to severe hypoglycaemia with equivalent frequency. For instance, the quarterly TTO values for severe daytime hypoglycaemia and non-severe daytime hypoglycaemia for the general population were 0.008 and 0.35. In general, as the frequency of the hypoglycaemia increased, the utility value decreased except for non-severe daytime hypoglycaemia and nocturnal hypoglycaemia.

Table 3 shows the mean disutility values for the hypoglycaemia events for each health state. The mean disutility value for severe hypoglycaemia in the GP respondents was 0.333 (SD 0.347) which was greater compared to severe hypoglycaemia in T2DM respondents (mean = 0.2409, SD: 0.2238). Comparing the data for both groups, it was concluded that daytime hypoglycaemia was associated with greater disutility values compared to nocturnal hypoglycaemia.

None of demographic factors (e.g. gender, age, marital status, education status, ethnicity, family history of diabetes) in the T2DM group significantly affected the final data analysis. However, the demographic factors like family history of diabetes and ethnicity were significantly associated ($P < 0.05$) with the final data analysis in the respondents from the GP. The interviewers and total interview times only significantly ($P < 0.05$) affected the final data analysis amongst GP respondents.

Discussion

In general, the negative impact of the varying severity of hypoglycaemia events on HRQoL in the Malaysian population are quantified by the utility value when measured using both approaches. The utility values were lower compared to similar studies from other countries (10, 11, 17). The mean utility value for well-controlled diabetes (without a hypoglycaemia event) in the general population in Malaysia was 0.643 (with TTO method) was lower compared to other studies (10, 11) with the mean value ranged between 0.819 (11) and 0.844 (10). Similarly, the mean utility value of severe hypoglycaemia occurring quarterly in Malaysia was 0.112 which was much more lower compared to one Canadian study which was 0.711 (11) and 0.787 (17). The lower utility value compared to other studies may be explained by different cultural norms (12). Culture influences the way respondents process information and make decisions in valuation tasks (18). The valuation of any health state is elicited within a specific cultural context because the respondents have to live in their respective health states in their current environment (18). Consequently, they might have different perceptions of their health state. Moreover, health utility values are sensitive to a country's healthcare system (12). Advances in medical technology and its diffusion throughout healthcare systems may influence respondents' preferences. Respondents may fear hypoglycaemia if they have difficulty accessing its management. Furthermore, the respondents' ages may have affected the results; they were mostly young and healthy (46 years versus 25 years) in the GP group, and some respondents had

Table 2 Respondents' profile in final data analysis

Social demographic characteristics	Total number of respondents	
	GP	T2DM
Gender, n (%)		
Male	43 (30.7)	45 (58.4)
Female	97 (69.3)	32 (41.6)
Age, mean (SD) years	25.74 (11.43)	54.44 (11.43)
Ethnic, n (%)		
Malay	104 (74.3)	34 (44.2)
Chinese	18 (12.9)	26 (33.8)
Indian	13 (9.3)	16 (20.8)
Others	5 (3.6)	1 (1.3)
Education Status, n (%)		
No formal education or primary	4 (2.9)	20 (26)
Secondary	23 (16.4)	39 (50.6)
Diploma and undergraduate	110 (78.5)	17 (22.1)
Postgraduate	3 (2.1)	1 (1.3)
Employment Status, n (%)		
Employed	33 (23.6)	45 (58.4)
Unemployed/ student	104 (74.3)	19 (24.7)
Retired	3 (2.1)	13 (16.9)
Marital Status, n (%)		
Single	114 (81.4)	9 (11.7)
Married	26 (18.6)	68 (88.3)
Mean diabetes knowledge assessment, (SD)	10.44 (3.20)	10.91 (2.56)
Diabetes history, n (%)		
Yes	10 (7.1)	77 (100)
No	130 (92.9)	
Family history of Diabetes, n (%)		
Yes	63 (45)	56 (72.7)
No	77 (55)	21 (27.3)

never experienced a hypoglycaemia event, hence they considered and imagined the effects to be more severe than in reality.

Theoretically, the utility value should be inversely proportional to the frequency of hypoglycaemia in the TTO and VAS approaches, as shown in the severe hypoglycaemia. However, this trend was not pronounced in the non-severe daytime and nocturnal hypoglycaemia due to the reason that the respondents valued one of the scenario in each type of hypoglycaemia in a block with the same frequency of attacks in all scenario. Subsequently, they might have thought that these were worse condition compared to baseline diabetes (without hypoglycaemia attack) as it was easier for the respondents to discriminate the scenario of hypoglycaemia with different frequency of attacks in a block. Therefore, the trends for non-severe hypoglycaemia were not inversely proportional to the frequency of hypoglycaemia in the TTO and VAS approaches. For instance, respondent “A” was required to elicit

a preference between non-severe nocturnal or daytime hypoglycaemia occurring once quarterly while respondent “B” received a block with non-severe daytime hypoglycaemia occurring once weekly and non-severe nocturnal hypoglycaemia occurring once monthly. In this scenario, respondent “B” value for each type of hypoglycaemia differently because the frequency of attacks was significantly different. However, the respondent “A” may give similar scores for each scenario of hypoglycaemia because the frequency of hypoglycaemia appears the same. However, the respondent “B” to elicit a higher value for non-severe nocturnal hypoglycaemia occurring once monthly because the respondent “B” elicits the hypoglycaemia scenario with different frequencies. Consequently, this value might be higher than the value given by the respondent “A” for non-severe nocturnal hypoglycaemia occurring once quarterly because the respondent “A” elicits the scenario of hypoglycaemia with similar frequencies. Thus, it was possible that the value of hypoglycaemia occurring once monthly became higher than once quarterly.

Severe hypoglycaemia was associated with greater disutility compared to non-severe hypoglycaemia in the TTO and VAS approaches. This may have been due to the burden and the complications of severe hypoglycaemia negatively affecting the respondents' preferences. For instance, the respondents may not prefer the hospitalization risk and coma which are possible complications in a scenario involving severe hypoglycaemia.

In theory, the utility value for nocturnal hypoglycaemia should be lower than daytime hypoglycaemia. Clinical studies show that nocturnal hypoglycaemia is more worrisome due to the sympatho-adrenal responses to hypoglycaemia being suppressed during sleep (19). The body is unable to react for self-treatment and this may cause more serious sequelae (19). However, in this study, the above theory was not demonstrated as expected. It is speculated that this could be caused by the fear of limitations to their daily or economic activities during daytime hypoglycaemia. For these respondents, nocturnal hypoglycaemia would happen at night and may not affect their daily activities.

The disutility values of hypoglycaemia in the TTO method were greater compared to the VAS method. TTO approach is vulnerable to coping effect, whereas VAS is not. Besides, the TTO method provided the respondents a chance to rank the states either for better or worse than dead. This approach may generate a value lower than 0 when in actuality, the state was valued worse than dead. VAS approach did not generate a value lower than 0.

T2DM respondents gave a higher utility score for hypoglycaemia events compared to GP respondents. Some studies suggested that people who have experienced a disease or disability condition tend to value that state more highly than those with not experience (20, 21) because they may have

Fig. 2 Mean utility values for hypoglycaemia according to severity and frequency using VAS method

experienced a hypoglycaemia event and understand the severity of hypoglycaemia. In addition, they might adapt to the condition or adjust themselves to the illness or disability, resulting in fewer losses in HRQoL than anticipated prior to any illness or disability.

The limitations to this study include the non-uniformity in the respondent's perception towards hypoglycaemia especially if they have never experienced it as explained above. Another limitation would be the sample size. The sample size

might not have represented accurately the preference of all Malaysians towards hypoglycaemia events as they were from Penang, one of the States in Malaysia; even though sample selection using face-to-face interviews should already reduce the variability inherent in the survey.

Conclusion

In summary, this research analysis contributed to the understanding of the impact and utilities of hypoglycaemia using the VAS and TTO methods and the factors that cause data exclusion. The findings show that any form of hypoglycaemia has a negative impact on the HRQoL in the general and T2DM population. They demonstrate the importance of preventing the development of hypoglycaemia, especially severe hypoglycaemia in patients with T2DM.

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Table 3 Mean disutility value per hypoglycaemic event for each health state

	Mean disutility value (SD)			
	GP		T2DM	
	VAS	TTO	VAS	TTO
Non-severe daytime event	0.0206 (0.0312)	0.0354 (0.0740)	0.0226 (0.0402)	0.0283 (0.0597)
Non-severe nocturnal event	0.0141 (0.0194)	0.0155 (0.0310)	0.0221 (0.0302)	0.0234 (0.0453)
Severe daytime event	0.2171 (0.1351)	0.3619 (0.3676)	0.2352 (0.1778)	0.1938 (0.1867)
Severe nocturnal event	0.1913 (0.1250)	0.3027 (0.3207)	0.2122 (0.1337)	0.2801 (0.2459)

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