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Editorial

AI in Healthcare: Applications and Challenges

Elaine Wan Ling Chan

The availability and complexity of data in healthcare provide endless opportunities to leverage artificial intelligence (AI) for more precise and efficient treatments for patient care. AI is defined as "the capacity of machines to mimic the cognitive function of humans"[1]. The term was first used in the 1950s and since then for many years, it had been tested and used to improve diagnostic test accuracy using a narrow type of AI called "computer aided diagnosis (CAD)".[1-2] Recently, with the evolution of AI and machine learning towards convolutional neural networks and deep learning, AI applications expanded further beyond diagnostics. It had the potential to transform patient care, administrative processes within healthcare providers and drug discovery. As compared to traditional analytics and clinical decision-making skills, AI algorithms are based on training data, providing unprecedented insights into diagnostics, patient care process, patient outcome and treatment variability.[1,3-4] In future, AI is poised to be the main engine that drives advancement across the care continuum, accelerated by the staggering rate at which the volume of available medical data continues to increase.

AI in healthcare generally refers to the use of machine to review, analyse, interpret and suggest solutions to complex medical problems based on medical data that was ingested in an automated manner. AI had been used in the diagnosis and treatment of diseases in which rule-based system was first developed in the 70s to diagnose blood-borne bacterial infections.[1,4] However, these rule-based systems do not have the precision of algorithmic systems developed using machine learning. Algorithmic clinical decision support systems could easily adapt to the changes in medical knowledge and are capable of handling huge data and knowledge based on genomic, proteomic and other 'omic-based' approaches to diagnosis and treatment. They are driving the era of probability and evidence-based medicine.[1-5]

As a collection of technologies, AI could be applied to both structured and unstructured healthcare data. Traditionally, expert system based on the 'if-then' rules were widely used for clinical decision support system. A series of rules in the field of study is constructed based on knowledge of human experts. However, most often when there are many rules, the rules will end up conflicting with each other. Moreover, if the domain knowledge changes, it is challenging and time-consuming to change the rules.[1] Hence, it is slowly being replaced by approaches based on machine learning algorithms. The most popular AI technique is machine learning, a statistical technique of training models with data. An example of simple machine learning models like the support vector machine is widely used for structured data in predicting the disease or treatment outcome based on a training dataset consisting of patient attributes. As the outcome variable is known, it is termed supervised learning.[1] A more complex form of machine learning is the neural network, mimicking the way neurons process signals with inputs, outputs, and weighted features, which associate input with outputs. It has been used for categorisation of structural data, for example in the determination of a patient risk of having a disease.[1,5] The most complex machine learning technique is deep learning. It contains many levels of features that predict the outcome within

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the neural network. Deep learning is commonly used in image processing for the detection of clinically relevant features in medical images beyond what that could be detected by the human eye. In addition, deep learning is also used for speech recognition as a form of natural language processing. The main application of natural language processing in healthcare involves the classification of clinical reports and published research articles. It is used to process the unstructured clinical notes, reports and conduct conversational AI.[1,5]

Nowadays, the primary and foremost use of AI in healthcare is through diagnosis of patients using medical imaging. Manual inspection of images obtained from imaging techniques such as X-Ray, MRI and CT Scan is often difficult to identify microscopic abnormalities, and this requires highly trained and skilled experts in the field. The demand for medical imaging is increasing and in future there will be a shortage of experts in the field.[2,6] However, with the advent of deep learning technologies in AI, AI will be a tool to fill the demand gap and enable better detection of abnormalities that would otherwise go undetected.[1] It is almost certain that in future radiology and pathology images will be analysed by a computer with the rapid advancement of AI in medical imaging. However, to ensure the effective adoption in clinical practice, it is paramount to ensure that AI findings are associated with clinically meaningful outcomes. The ability of the AI to distinguish benign abnormalities and clinically relevant lesions are crucial in reducing a false positive rate that might come as a cost of better image sensitivity.[6]

AI has also emerged in the field of drug discovery. The route for a new drug from research laboratories to patient is a costly, complex, and long one. In the past years, there has been a substantially large amount of data available in assessing drug compound activities, but mining of the large-scale chemistry data is needed to search for potential drug compounds.[4] AI had been used to streamline the drug discovery and drug repurposing processes to significantly cut both the cost and time to market for new drugs. AI can recognise hit and lead compounds, predict new therapeutic use, shorten the time required to validate drug target, and assist in the optimisation of the drug structure design. AI had been effectively used in different parts of drug discovery, including chemical synthesis, and drug design, screening, and repurposing. AI not only speeds up the time of the product to market, but it will also improve the quality and overall safety of the production process, making it more cost-effective.[4,7]

Another interesting application of AI in healthcare is genomics and precision medicine. Recently, genetic information from a population pool is widely available due to the cheaper and easier access to full genome sequencing. With the genetic information, AI algorithms could be used to find correlations and predict treatment responses for individual patients. In addition to genetic information, other biomarkers such as protein expression, metabolic profile and gut microbiome could be analysed with AI for precision medicine. Precision medicine is used to customise the treatment plan for an individual based on the individual's genetic make-up and surrounding environment. Nowadays, massive amount of data from an individual is made available with the use of wearable sensors and "OMICS" whereby AI could analyse and interpret these data with incredible efficiency. AI algorithms such as machine learning, deep learning and artificial neural network are the primary tools behind the development of precision medicine.[1] Recently, promising results had been shown in predicting

the disease risk of cancer and cardiovascular disease using prediction algorithms with high degree of accuracy and precision.[1,4,8]

AI has also been used to improve the administrative processes in healthcare for example, clinical documentation, management of medical records and claims processing. Machine learning algorithms which use probabilistic matching to verify claims could save time, money , effort of insurers, providers and governments.[1] Chatbot had also been used for appointment bookings and telehealth though there are concerns on the willingness of patient in revealing confidential information and health condition to a machine.[9]

Overall, AI can transform many areas of healthcare and addresses imperative healthcare challenges. Accumulating evidence have shown that the performance of AI algorithms is on par or better than experts in analysing medical images and providing diagnosis or treatment recommendations based on symptoms and biomarkers from electronic medical records.[1,4] However, in the past, patient care decision had been made almost exclusively by humans. Moreover, AI algorithms like deep learning used in image analysis are not possible to be explained. There is no explanation on how an image has to a diagnosis of cancer as compared to that determined by a clinician.[1] Hence, the use of AI in healthcare involves ethical issues that need to be addressed like the lack of empathy between AI and patients, the questions of responsibility, transparency, and data privacy.[1,4]

For AI to be adopted widely in clinical practice, the developed AI software needs to be approved by regulators, integrated into the electronic health record system, standardised in a manner with similar product function in a similar fashion. One of the main challenges is the current perspective that AI will replace clinicians. This must be changed to promote wider adoption of AI in healthcare settings. In fact, AI will augment the effort of clinicians to care for patients. Unique human skills such as empathy and persuasion will be taken on by human clinicians while AI will provide the information needed.[1,10]

There will be many challenges with AI in healthcare ranging from ethical, medical to technological. Eventually, most of these challenges faced in adoption of AI in healthcare setting will be overcome. However, the ethical challenges will take longer than it will take for the technologies themselves to mature. Hence, it is expected to see limited use of AI in the next 5 years but more extensive use within 10 years.

Keywords: *Artificial Intelligence, healthcare applications, machine learning, diagnosis*

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Review Article

Serum visfatin in Type 2 Diabetes Mellitus - A systematic review and meta-analysis

Shivani Harikrishnan[1,2], Sangeetha Shyam[3,4], Suan Phaik Khoo[5]

Recent studies have theorised that visfatin plays a significant role in the development and progression of Type 2 Diabetes Mellitus (T2DM). Some studies indicate that levels of serum visfatin are increased in subjects with T2DM whereas other studies dispute this claim. Since the results of these studies remain inconsistent, a systematic review and meta-analysis were performed. A search of PubMed, Ebsco-MEDLINE, Scopus, Science Direct, and Cochrane was conducted up till February 2019. Data analysis was performed using Review Manager 5.3. The standardised mean difference (SMD) with a 95% confidence interval (CI) was used to pool the effect size. The Newcastle Ottawa scale (NOS) was used to evaluate bias in the selected studies and a funnel plot was used to assess publication bias. A total of 17 studies were included in this systematic review and meta-analysis. Overall, levels of serum visfatin in subjects with T2DM were significantly higher when compared to the healthy adults (SMD: 1.68 95% CI [1.22,2.14], p<0.00001, I^2=92%). Sensitivity and subgroup analyses did not decrease heterogeneity. Among subjects with T2DM, those with additional comorbidity showed moderately increased levels of serum visfatin when compared to the subjects without comorbidity (SMD: 0.73 95% CI [0.14,1.32], p< 0.00001, I^2=92%). Sensitivity and subgroup analyses performed did not significantly decrease heterogeneity. Levels of serum visfatin are increased in subjects with T2DM when compared to healthy adults. Levels of serum visfatin are increased in subjects with T2DM with comorbidity when compared to subjects with T2DM without comorbidity. However, these findings must be interpreted with caution as high heterogeneity (I^2=92%) was observed.

Keywords: *Serum visfatin, Type 2 Diabetes Mellitus, Systematic Review, Meta-Analysis*

Introduction

Type 2 Diabetes Mellitus (T2DM), a chronic metabolic disorder, is one of the most common diseases in the world today with over 500 million individuals diagnosed till date[1]. It is characterised primarily by insulin resistance and pancreatic beta cell dysfunction[2]. Individuals with T2DM are more susceptible and often present with different forms of acute and chronic complications and comorbidities. This can substantially lower their quality of life, generate an enormous social and economic burden, and can sometimes even lead to a premature death[2,3]. The increased morbidity and mortality that is commonly seen in individuals with T2DM can be attributed to the insidious onset and late recognition characteristics of this disease[3].

Previously known as a disease of affluence due to its predominance in the western world, T2DM is now quickly spreading all over the globe due to rapid urbanisation. With urbanisation comes environmental and lifestyle changes, some of which have been known to trigger the development of T2DM. A sedentary lifestyle and a poor diet have been shown to increase Body Mass Index (BMI). These factors coupled with age, gender and ethnicity increase the risk of T2DM[4,5]. Therefore, it is important to identify and study the potential diagnostic and prognostic factors, as well as therapeutic targets in order to slow down the incidence of this disease.

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Adipose tissue has recently been described as a highly active endocrine and metabolic organ with an important role in lipid and glucose metabolism. Adipose tissue produces hormones and cytokines, which are collectively known as 'adipocytokines or adipokines'. These include tumor necrosis factor-alpha, adiponectin, leptin, resistin and visfatin[4,6].

Visfatin, also known as pre-B cell colony enhancing factor (PBEF) and nicotinamide phosphoribosyl transferase (Nampt), is a newly discovered adipocytokine[7]. Fukuhara et al, demonstrated that visfatin has insulin-mimetic effects such as the inhibition of hepatic glucose release, an increase in glucose uptake in myocytes and adipocytes, and an increase in triglyceride synthesis[7]. However, since these results could not be subsequently confirmed, this paper was later retracted[7]. Present-day data proposes that visfatin is important to normal insulin secretion although this mechanism and its association with the development and progression of T2DM remain unclear[8].

The cause – effect relationship between T2DM and visfatin is a controversial one[8]. Some of this controversy stems from whether or not there is a rise in levels of serum visfatin in individuals with T2DM. While some studies show compelling evidence that levels of serum visfatin are increased in subjects with T2DM[9-23] when compared to healthy adults, others have reported no significant association[24,25].

In order to understand whether levels of serum visfatin are different between subjects with T2DM and healthy adults, and to evaluate if the presence of an accompanying comorbidity has an effect on these levels, this comprehensive systematic review and meta-analysis was conducted. Additionally, this study is a step towards evaluating the potential of serum visfatin as a prognostic and diagnostic marker for T2DM to complement existing therapy or diagnostics.

Methodology

Literature Search

The PRISMA 2009 protocol for reporting systematic reviews and meta-analysis was prospectively followed. Ethical approval was not sought since there was no need to handle individual patient data. PubMed, Ebsco MEDLINE, Science Direct, Scopus, and Cochrane were systematically searched using a Boolean code - 'serum' AND 'visfatin' AND 'type 2 diabetes mellitus'. The following filters were added to narrow down the results of our search. The English filter was applied in PubMed and the search was confined to research articles in ScienceDirect. For Ebsco MEDLINE, the search was limited to academic journals, all adults above the age of 19, English, and with the major heading including the keywords diabetes mellitus, type 2. In Scopus, the English language and only research articles filter were used. No filters were applied in the Cochrane database.

Study Selection

Two reviewers (SH and SGS) independently performed a thorough eligibility assessment based on the title and abstract of a paper following the inclusion and exclusion criteria which are as follows. For a study to be included in our meta-analysis it must (1) be in English (2) involve both healthy participants and those diagnosed with Type 2 Diabetes Mellitus and report serum levels of visfatin as such separately (3) involve adults over the age of 18 (4) be an observational study. Any studies that included a Type 2 Diabetic group and a group with additional comorbidities and did not report serum

visfatin levels separately were excluded. Studies that did not use a healthy control group and review articles, conference abstracts, letters, and book chapters were excluded as well. Any disagreements on the admissibility of a paper were resolved by a third reviewer (SPK).

Data Extraction

A predesigned data extraction form was used to collect comprehensive information from each included study. Details collected are as follows - (1) author, (2) location (3) gender (4) age (5) study design (6) comorbidities (if any) (7) participant numbers (case/control) (8) method of measurement of visfatin (9) T2DM definition (10) BMI (11) HbA1c levels 1(12) serum visfatin in healthy controls (13) visfatin levels in T2DM (14) visfatin levels in T2DM plus comorbidities (if there are any comorbidities).

Assessment of quality

The quality of included eligible studies regarding the role of serum visfatin levels in T2DM was evaluated based on Newcastle–Ottawa Scale (NOS), which assesses a study based on selection, the comparability of the groups, and the ascertainment of the exposure or outcome of interest with the use of a rating system. One star is allocated when a feature of quality is present, and total scores are ranged between 0 and 9. Scores between 0 to 3 were regarded as low-quality studies, 4 to 6 were regarded as moderate quality studies and 7 to 9 were regarded as high-quality studies.

Conversion of Data

The unit of measurement for the levels of serum visfatin in this study was ng/ml with mean ±SD for statistical expression. Since not all studies were reported in this format, some units had to be converted. Three studies[12,16,25] that presented their data as median (interquartile range) were converted to mean ±standard deviation (SD) using a method devised by Hozo et al[26]. One study[21] that expressed levels of serum visfatin in µg/l was converted to ng/ml using standard measurements of conversion. Another study[19] which expressed the levels of serum visfatin as mean ± standard error of the mean (SEM) was converted to the preferred format of mean ± SD using the Review Manager Calculator[27]. Another study[21] that presented its data in log ng/ml format was converted to ng/ml using the inverse function in a calculator. Data expressed in a box plot was extracted by two independent reviewers before being used in this study. The data from the boxplot[25] is expressed as median (interquartile range) which was then converted to mean ±SD using an equation devised by Hozo et al[26].

Statistical Analysis

Data analysis was performed using Review Manager 5.3. All data were calculated as Standard Mean Deviation (SMD) with 95% CI. SMD was used as not all our data had been originally expressed using the same unit of measurement. The effect size was calculated using the random-effects model as we anticipated heterogeneity between the papers. Heterogeneity was assessed by the I^2 test. The results of the I^2 test were interpreted according to Cochrane Handbook of Systematic reviews and meta-analysis which suggest that 0% to 40% indicates heterogeneity might not be important, 30% to 60% may represent moderate heterogeneity, 50% to 90% may represent substantial heterogeneity and 75% to 100% represents considerable heterogeneity.

To investigate any specific source of heterogeneity, a sensitivity analysis was carried by sequentially removing each study. This was done in order to evaluate the influence of a study on the pooled results. If heterogeneity remained high, a subgroup analysis was undertaken to

find the root cause. Secondary assessments were made by performing comparative sub-group analysis to identify potential source of heterogeneity within T2DM subjects. This included sub-group analysis of T2DM subjects differing by age groups (≥ 50 years and < 50years), gender, study location (Europe, Asia, Africa), duration of T2DM, glycaemic control, treatment modality presence of obesity (BMI ≥ 25 and ≥ 30), cardiovascular disease and metabolic syndrome, when such information was explicitly available in literature.

Publication Bias

We used the funnel-plot method to test for publication bias. In this method, the difference in standard mean changes is plotted against their standard errors.

Results

Search results

A search of the aforementioned databases resulted in 336 citations. After adjusting for 73 duplicates, we ended up with 263 citations. Out of this, 243 papers were excluded after reviewing abstracts as they did not meet inclusion criteria. The remaining 20 studies were examined more closely, and 3 articles were further excluded. The 17 studies that fit our criteria were included in our meta-analysis. Out of these 17 studies, 8 papers had additional information to carry out a meta-analysis to determine serum visfatin levels in those with T2DM and comorbidities. Figure I shows the PRISMA flowchart for this analysis.

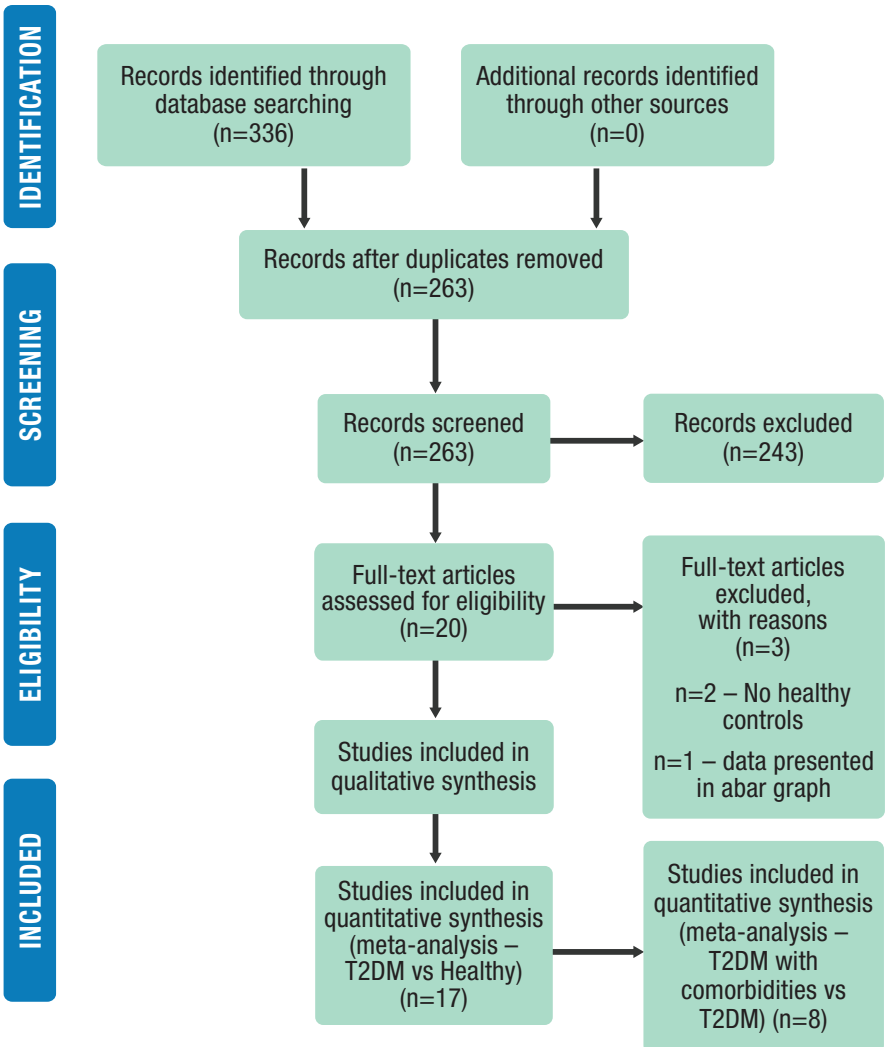

Figure I: PRISMA flowchart

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Characteristics of included studies

Out of the 17 studies that were selected for this meta-analysis, 15 were cross-sectional studies and two were open-labelled drug therapy trials. These studies involved a total of 1,445 participants out of which 763 had T2DM. The remaining 682 participants were healthy controls. Two studies explored the effects of drugs: thiazolidinedione's[17] and rosiglitazone[21] on levels of serum visfatin in subjects with T2DM and healthy adults. Fifteen studies explored the relationship of levels of serum visfatin in T2DM when compared to healthy adults. The summary of key findings of papers only comparing levels of serum visfatin in subjects with T2DM and healthy adults are shown in Table I.

Table I: Characteristics of studies that compare levels of serum visfatin in subjects with T2DM and healthy adults

S. No/ Ref No	Author/Year	Location	Study Design	Participants (Case/Control)	Method of visfatin measurement	T2DM Definition	Serum visfatin level in patients without T2DM (ng/ml) mean+SD	Serum visfatin level in patients with T2DM (ng/ml) mean+SD	Newcastle-Ottawa scale
1 [9]	Hetta et al, 2018	Saudi Arabia	Hospital Based Cross Sectional	80/40	EIA	WHO criteria for diagnosis of diabetes (WHO 2007)	19.0±8.2	40.33±9.98	5
2 [10]	Legakis et al,2016	Greece	Cross sectional	37/43	EIA	75g OGTT	2.9±0.7	5.0±2.1	5
3 [11]	Esteghamati et al,2010	Iran	Cross sectional	76/76	ELISA	Self-Reported	3.6±2.2	5.5±2.4	5
4 [12]	Retnakaran et al,2008	Thailand	Cross sectional	50/79	ELISA	Self-Reported	2.2±0.5	2.8±0.7	6
5 [13]	Lopez-Bermejo et al,2006	Spain	Prospective Study	35/118	EIA	American Diabetes Association	15.0±0.8	17.0±2.0	5
6 [15]	Celebi et al,2017	Turkey	Cross sectional study	20/20	ELISA	American Diabetes Association (2003)	0.6±0.6	3.2±2.2	5
7 [21]	McGee et al,2011	Coventry	Open labeled drug therapy trial	30/34	EIA	Self-Reported	1.1±0.1	1.4±0.1	4
8 [20]	El Shaer et al,2012	Egypt	Cross sectional	60/20	ELISA	Self-Reported	14.4±4.2	22.9±17.5	5
9 [17]	Hammarstedt et al,2006	Sweden, Finland	Open labeled drug therapy trial	7/6	EIA	Self-Reported	21.5±8.3	42.0±19.9	4

Abbreviations:

ELISA-enzyme-linked immunosorbent assay; EIA: enzyme immunoassay; OGTT - oral glucose tolerance test.

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Out of these 15 studies, eight studies also explored the levels of serum visfatin in T2DM patients who had a comorbidity. Out of the eight studies, the comorbidity in two studies was metabolic syndrome[14,18], four studies with cardiovascular disease[16,22-24] and two studies with obesity[19,25]. The summary of key findings from papers comparing levels of serum visfatin in subjects with T2DM with a comorbidity and subjects with T2DM without a comorbidity are shown in Table II. The NOS score of all the studies assessed was between four and six indicating moderate quality.

Table II: Characteristics of studies that compare levels of serum visfatin in subjects with T2DM with comorbidity and subjects with T2DM without comorbidity

S. No/ Ref No	Author/ Year	Location	Study Design	Comorbidity	Participants [Case (T2DM)/ Case with Comorbidity/ Control]	Method of visfatin measurement	T2DM Definition	Serum visfatin level in healthy control (ng/ml)	Serum visfatin level in patients with T2DM (ng/ml)	Serum visfatin in patients with T2DM and comorbidity	Newcastle-Ottawa scale
1 [14]	Ahmed et al,2015	Saudi Arabia	Cross sectional	Metabolic syndrome	39/48/29/	ELISA	Self-Reported	18.4±6.0	28.2±15.1	58.9±29.9	5
2 [16]	Bilovol et al,2020	Ukraine	Cross sectional	Arterial Hypertension	61/125/20	ELISA	American Diabetes Association	17.0±2.0	39.0±3.5	42.0±2.7	5
3 [24]	Ahmed et al,2018	Egypt	Cross sectional	Cardio-Vascular disease	40/40/20	ELISA	Self-Reported	1.2±0.20	1.4±0.7	3.9±3.3	5
4 [18]	Haddad et al,2018	Iraq	Cross sectional	Metabolic Syndrome	44/22/22	EIA	WHO criteria (Alberti Zimmet, 1998)	52.5±14.1	63.7±8.3	56.0±10.6	6
5 [22]	Motawi et al,2014	Egypt	Cross sectional	Cardiovascular Disease	44/46/60	EIA	Self-Reported	17±4.1	29.8±6.3	41.0±7.9	5
6 [23]	Alghasham et al,2008	Saudi Arabia	Cross sectional	Microangiopathy	29/33/22	ELISA	American Diabetes Association criteria 1998	8.9±4.2	14.3±5.8	10.8±6.3	6
7 [25]	Kara et al,	Turkey	Cross sectional	Obesity	20/25/20	ELISA	American Diabetes Society criteria	6.0±0.5	8.0±1.0	11.3±2.8	6
8 [19]	El Mesallamy et al 2010	Egypt	Cross sectional	Obesity	37/19/19	ELISA	Self-Reported	9.4 + 8.6	25.9±3.4	45.4±20.1	6

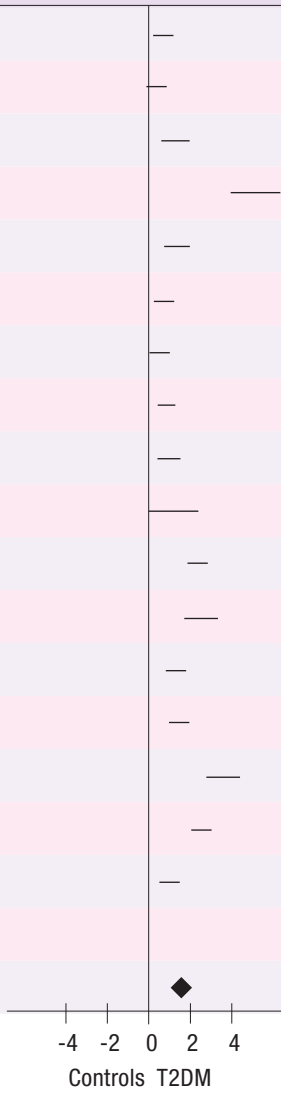
Meta-analysis results

The results of the meta-analysis are discussed under two sections (i) Levels of serum visfatin in subjects with T2DM vs healthy adults and (ii) Levels of serum visfatin in subjects with T2DM with and without a comorbidity

(i) Levels of serum visfatin in subjects with T2DM vs healthy adults

There is a significant increase in levels of serum visfatin in subjects with T2DM in comparison to healthy adults (SMD: 1.68, 95% CI [1.22,2.14], P<0.00001). However, pooled studies showed significant heterogeneity ($I^{\wedge 2}$= 92%). (Figure II)

	Type 2 Diabetes Mellitus			Healthy Control				Std Mean Difference	Std Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Ahmed 2015	28.2	15.1	39	18.4	6	28	6.2%	0.80 [0.29, 1.30]	
Ahmed 2018	1.44	0.71	40	1.17	0.2	20	6.1%	0.45 [-0.09, 0.99]	
Alghasham 2008	14.3	5.77	29	8.92	4.16	22	6.0%	1.03 [0.44, 1.62]	
Bilovol 2020	39	3.5	61	17	2	20	4.6%	6.80 [5.61, 7.99]	
Celebi 2017	3.2	2.2	20	0.6	0.6	20	5.7%	1.58 [0.86, 2.30]	
El Mesallamy 2010	25.9	20.9247	37	9.37	8.63062	19	6.0%	0.92 [0.34, 1.50]	
El Shaer 2012	22.9	17.5	60	14.4	4.2	20	6.1%	0.55 [0.03, 1.06]	
Esteghamati 2010	5.49	2.4	76	3.58	2.2	76	6.4%	0.83 [0.49, 1.16]	
Haddad 2018	63.71	8.3	44	52.46	14.05	22	6.1%	1.05 [0.51, 1.60]	
Hammarstedt 2006	42	19.9	7	21.5	8.3	6	4.5%	1.21 [-0.01, 2.44]	
Hetta 2018	40.33	9.98	80	19.03	8.22	40	6.2%	2.24 [1.77, 2.72]	
Kara 2014	8	1	20	6	0.5	20	5.4%	2.48 [1.64, 3.32]	
Legakis 2016	4.968	2.138	37	2.891	0.6168	43	6.2%	1.35 [0.86, 1.84]	
Lopez-Bermejo 2006	17	2	35	15	0.833	118	6.3%	1.66 [1.24, 2.08]	
McGee 2010	1.36	0.095	30	1.056	0.0725	34	5.5%	3.58 [2.78, 4.39]	
Motawi 2014	29.82	6.26	44	17	4.11	60	6.1%	2.48 [1.96, 3.00]	
Retnakaran 2008	2.75	0.695	50	2.22	0.4533	79	6.4%	0.94 [0.57, 1.32]	
Total (95% CI)			709			647	100.0%	1.68 [1.22, 2.14]	



Heterogeneity. Tau* = 0.83, Chi* = 194.80, df = 16 (P < 0.00001), I* = 92%
Test for overall effect Z = 7.12 (P < 0.00001)

Figure II: Data analysis - Levels of serum visfatin in subjects with T2DM vs healthy adults

Sensitivity Analysis

Sensitivity analysis was conducted by excluding each study one by one. This was done in order to evaluate the influence of each study on the pooled results. Only one study (Bilovol 2020[16]) slightly reduced the heterogeneity (from 92% to 87%). Sensitivity analysis of included studies did not significantly decrease pooled heterogeneity.

Subgroup Analysis

BMI - Subjects with T2DM were separated into subgroups to reflect overweight (BMI ≥ 25) and obese (BMI ≥ 30) categories as per the World Health Organization (WHO) definition[28]. Subjects with T2DM with BMI greater ≥ to 25 showed a significant increase in levels of serum visfatin compared to healthy adults (SMD: 1.42, 95% CI [1.04,1.80]) as did T2DM cases with BMI < 25 (SMD: 4.62[0.38,8.85]). Levels of serum visfatin were significantly higher in subjects with T2DM compared to healthy adults when the BMI of the subjects with T2DM was ≥ 30 (SMD: 1.53, 95% CI [1.02,2.04]) as well as when it was ≤ 30 (SMD: 2.11, 95% CI [1.15,3.06]).

Age - Subgroup analysis based on age was separated into different age groups reflecting the advancement of age among subjects with T2DM. Subjects with T2DM who were ≥ 50 years of age (SMD: 1.88, 95% CI [1.26,2.50]) and < 50 years of age (SMD: 1.53, 95% CI [0.74,2.32]) showed a significant increase in levels of serum visfatin when compared to healthy adults. Subjects with T2DM who were ≥ 55 years of age (SMD: 1.36, 95% CI [0,84,1.87]) and < 55 years of age (SMD: 1.89, 95% CI [1.26,2.53]) showed a significant increase in levels of serum visfatin when compared to healthy adults. Subjects with T2DM who were ≥ 60 years of age (SMD: 1.86, 95% CI [0.76,2.96]) and < 60 years of age (SMD: 1.75, 95% CI [1.22,2.28]) showed a significant increase in levels of serum visfatin when compared to healthy adults.

Gender - Groups with more women subjects with T2DM (SMD: 1.36, 95% CI [0.52, 2.20]) and groups with more men subjects with T2DM (SMD: 1.94, 95% CI [1.29,2.58] showed significantly higher levels of serum visfatin when compared to healthy adults.

Location of Study - Subjects with T2DM in studies conducted in Europe (SMD: 2.87, 95% CI [1.41,4.32], Asia (SMD: 1.32, 95% CI [0.90,1.74]) and Africa (SMD: 1.10, 95% CI [0.15,2.05]) have significantly higher levels of serum visfatin compared to healthy adults.

Duration of T2DM - Subjects who were described as newly diagnosed with T2DM (SMD: 1.11, 95% CI [0.59,1.63]) and subjects as having had a previous/ long-standing diagnosis of T2DM (SMD: 2.06, 95% CI [1,40,2.72]) had significantly increased levels of serum visfatin when compared to healthy adults.

HbA1c Levels - Subjects with T2DM with HbA1c levels ≥ to 7% (SMD: 1.48, 95% CI [0.85,2.12]) and < 7% (SMD: 2.45, 95% CI [1.15,3.74]) had significantly increased levels of serum visfatin in comparison to healthy adults.

Treatment Modality - Subjects with T2DM in studies using participants using insulin therapy (SMD: 1.29 [0.60,1.98]) and subjects in studies who used participants using only oral hypoglycemics (SMD: 1.77, 95% CI [1.03,2.51]) had significantly increased levels of serum visfatin when compared to healthy adults.

The results of the subgroup analysis are summarized in Table III.

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Table III: Subgroup analysis – Levels of serum visfatin in subjects with T2DM vs healthy participants

SUBGROUP	CATEGORY	SMD	95% CI	I^2
BMI	≥25	1.42	[1.04,1.80]	86%
	<25	4.62	[0.38,8.85]	97%
	≥30	1.53	[1.02,2.04]	86%
	<30	2.11	[1.15,3.06]	94%
Age	≥50	1.88	[1.26,2.50]	93%
	<50	1.53	[0.74,2.32]	91%
	≥55	1.36	[0.84, 1.87]	73%
	<55	1.89	[1.26,2.53]	93%
	≥60	1.86	[0.76,2.96]	81%
	<65	1.75	[1.22,2.28]	93%
Gender	Men	1.94	[1.29,2.58]	94%
	Women	1.36	[0.52,2.20]	92%
Location of Study	Europe	2.87	[1.41,4.32]	95%
	Asia	1.32	[0.90,1.74]	82%
	Africa	1.10	[0.15,2.05]	92%
Duration of T2DM	Newly Diagnosed	1.11	[0.59,1.63]	45%
	Established	2.06	[1,40,2.72]	94%
HbA1c Levels	≥7%	1.48	[0.85,2.12]	89%
	<7%	2.45	[1.15,3.74]	95%
Treatment Type	Insulin	1.29	[0.60,1.98]	89%
	Oral Hypo-glycemic	1.77	[1.03,2.51]	92%

(ii) Levels of serum visfatin in subjects with T2DM with and without a comorbidity

There is a moderate increase in the levels of serum visfatin in subjects with T2DM with a comorbidity, compared to subjects with T2DM without a comorbidity. (SMD: 0.73, 95% CI [0.14,1.32], P<0.00001). However, pooled studies showed high heterogeneity (I^2=92%) (Figure III.)

	T2DM with comorbidities			T2DM				Std Mean Difference	Std Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Ahmed 2015	58.9	29.9	48	28.2	15.1	39	12.7%	1.25 [0.78, 1.71]	
Ahmed 2018	3.92	3.32	40	1.44	0.71	40	12.7%	1.02 [0.56, 1.49]	
Alghasham 2008	10.81	6.29	33	14.3	5.77	29	12.5%	-0.57 [-1.08, -0.06]	
Bilovol 2020	42	2.6667	125	39	3.5	61	13.2%	1.01 [0.68, 1.33]	
El Mesallamy 2010	45.4	20.05094	19	25.9	20.9247	37	12.2%	0.93 [0.35, 1.51]	
Haddad 2018	56.03	10.58	22	63.71	8.3	44	12.4%	-0.83 [-1.37, -0.30]	
Kara 2014	11.25	2.75	25	8	1	20	11.7%	1.48 [0.81, 2.15]	
Motawi 2014	41.03	7.86	46	29.82	6.26	44	12.7%	1.56 [1.09, 2.03]	
Total (95% CI)			358			314	100.0%	0.73 [0.14, 1.32]	

Heterogeneity. Tau* = 0.66, Chi* = 83.89, df = 7 (P < 0.00001), I* = 92%
Test for overall effect Z = 2.43 (P = 0.02)

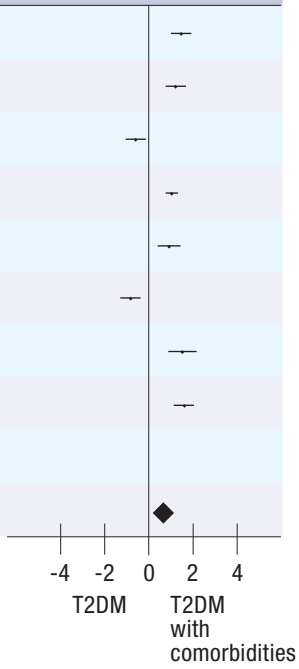

Figure III: Data Analysis - Levels of serum visfatin in subjects with T2DM with a comorbidity vs subjects with T2DM without a comorbidity

Sensitivity Analysis

Only two studies (Algasham 2008 and Haddad 2018) slightly reduced the heterogeneity of the pooled studies (from 92% to 79% and from 92% to 89% respectively). Sensitivity analysis of included studies did not significantly decrease pooled heterogeneity.

Subgroup Analysis

Obesity - Subjects with T2DM with a comorbidity showed significantly higher levels of visfatin when compared to subjects with T2DM without obesity. (SMD: 1.18, 95% CI [0.65,1.71]).

Cardiovascular Disease - Subjects with T2DM with cardiovascular disease showed moderately higher values of visfatin compared to subjects with T2DM without a comorbidity. (SMD: 0.76, 95% CI [-0.03,1.56]).

Metabolic Syndrome - Subjects with metabolic syndrome and T2DM showed slightly higher values of visfatin compared to subjects with T2DM without a comorbidity (SMD: 0.21, 95% CI [-1.83,2.25]).

These results are summarized in Table IV.

Table IV: Sub-group analysis: Level of serum visfatin in subjects with T2DM with a comorbidity vs subjects with T2DM without a comorbidity

SUBGROUP	CATEGORY	SMD	95% CI	I^2
Type of Comorbidity	Obesity	1.18	[0.65, 1.71]	32%
	Cardiovascular Disease	0.76	[-0.03, 1.56]	92%
	Metabolic Syndrome	0.21	[-1.83, 2.25]	97%

Publication Bias

Visual inspection of the funnel plot revealed asymmetry. Hence, publication bias cannot be excluded, and it cannot be established that a non-publication of negative or inconclusive data did not impact this meta-analysis (Figure IV).

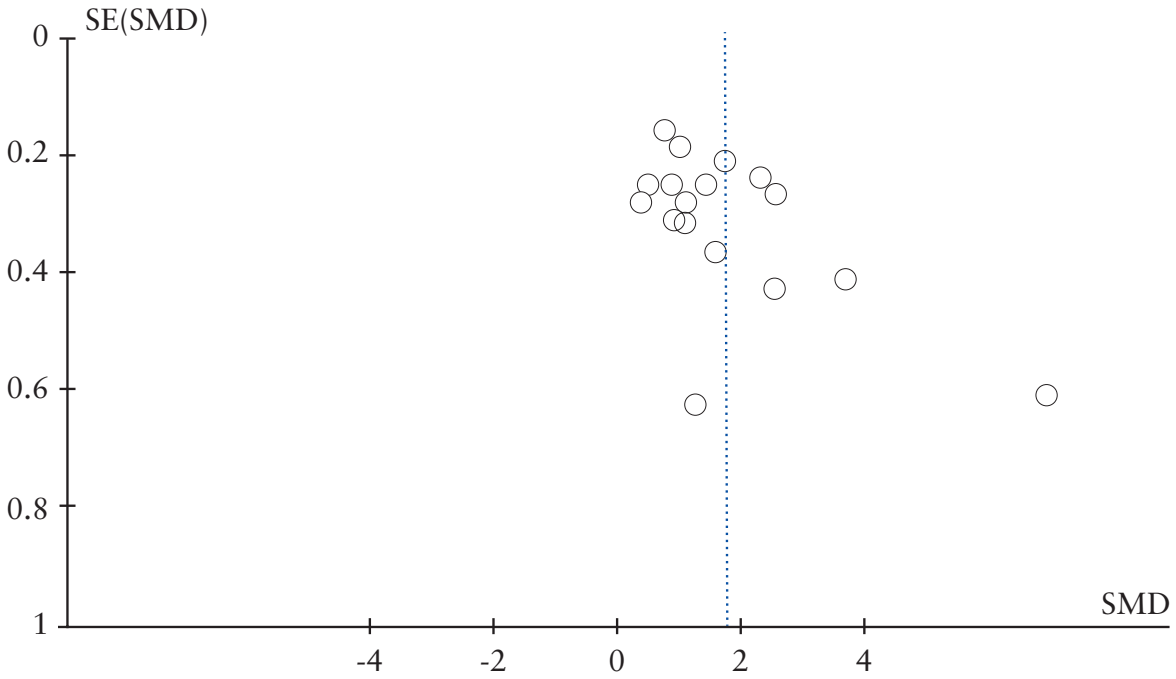

Figure IV: Funnel plot indicative of publication bias

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Discussion

The results of this study showed an increased level of serum visfatin in T2DM groups when compared to healthy controls (SMD: 1.68, 95% CI: [1.22, 2.14]). These increased levels of serum visfatin could be due to the effects of hyperglycaemia. One study found that an infusion of glucose caused an increase of circulating visfatin levels[29]. Likewise, Lopez et al. showed that in individuals with poor insulin secretion there was an increase in visfatin when an intravenous glucose tolerance test was performed[13]. Moreover, a meta-analysis showed a positive correlation between visfatin and insulin resistance which is a core factor in the development of T2DM[30]. This information indicates that in a hyperglycaemic environment, visfatin production can be stimulated. Since individuals with T2DM have hyperglycaemia because of insulin resistance or beta cell dysfunction, this could lead to the rise in serum levels of visfatin in T2DM.

To understand the high heterogeneity in this study (I^2=92%), a sensitivity analysis was performed by sequentially excluding each study one at a time. The sensitivity analysis performed showed that the exclusion of any included study did not significantly decrease or negate heterogeneity. One study had an effect size that was far apart from the effect sizes of the rest of the studies[16]. A sensitivity analysis undertaken to exclude this study[16] showed a small decrease in heterogeneity (from 92% to 87%). This indicates that while this study contributes to heterogeneity, it is not its root cause. Therefore, subgroup analyses were performed to investigate the origin of heterogeneity.

This study found an increase in levels of serum visfatin in T2DM patients regardless of their range of BMI. A study by Esteghmati et al inferred that visfatin levels are increased in T2DM independent of BMI. This was also reported by a meta-analysis[30] which suggested that the interaction between visfatin and glucose levels is not influenced by being overweight or obese.

The current meta-analysis found that serum visfatin levels are increased significantly in both subgroups containing subjects who use insulin and subjects who use oral hypoglycaemics. This correlates with studies done by Chen et al and Kadoglou et al which showed that insulin does not impact visfatin synthesis in adipocytes and as a result, there is no difference in serum levels of visfatin between type 2 diabetic subjects treated with insulin infusion or oral hypoglycaemic agents[31,32].

In T2DM, beta cells of the pancreas start to deteriorate due to over exertion because of increased insulin secretion to compensate for insulin resistance[4]. This study shows that serum visfatin levels are increased regardless of whether the subject with T2DM was newly diagnosed or had a previous T2DM diagnosis. It is theorised that serum visfatin could be a product of beta cell deterioration, which is also commonly seen even in newly diagnosed type 2 diabetics[13]. HbA1c level of more than 7% is considered to be linked with beta cell deterioration[33] and the production of visfatin is thought to correlate with beta cell dysfunction. However, this study showed that serum visfatin levels are increased regardless of whether HbA1c levels are <7% or >7%. However, this could simply be because of no correlation between visfatin and HbA1c levels[34].

In subjects with T2DM with a comorbidity, there is an increase in the level of serum visfatin when compared to subjects with T2DM without a comorbidity (SMD: 0.73, 95% CI: [0.14, 1.32]). However, there was considerable pooled heterogeneity (92%).

To understand the persistent high heterogeneity (I^2=92%), a sensitivity analysis was performed. The sensitivity analysis performed showed that the removal of any included study did not significantly decrease or negate heterogeneity. Two studies had effect sizes far apart from the effect sizes of the rest of the studies[18,23]. The sensitivity of these studies showed a small decrease in heterogeneity (from 92% to 87%[18] and from 92% to 89%[23]). This indicates that while these studies may contribute to heterogeneity, they are not its root cause. Therefore, subgroup analyses were done to investigate the origin of heterogeneity.

In subjects with T2DM and obesity, the levels of serum visfatin were shown to be significantly increased when compared to T2DM subjects without a comorbidity (SMD: 1.18, 95% CI [0.65,1.71]). Increased abdominal visceral fat has been thought to produce visfatin[7]. In addition to this, the increased adipose tissue mass seen in obesity is known to produce adipocytokines like visfatin[4]. This could be the cause of the increased levels of serum visfatin as seen in T2DM complicated with obesity.

In subjects with T2DM and cardiovascular disease, levels of serum visfatin are moderately increased in comparison to subjects with T2DM without a comorbidity. Visfatin in addition to being expressed by adipocytes, is also expressed by inflammatory cells such as macrophages. In cardiovascular disease, more specifically coronary artery disease, the levels of serum visfatin have been described to correlate with the circulating inflammatory markers present[35]. Additionally, one study found an increased expression of visfatin in macrophages around areas with carotid plaques[36]. This increased expression of visfatin could contribute to the increased levels of serum visfatin in subjects with T2DM and cardiovascular disease that is seen in this study.

This study showed that in subjects with T2DM with metabolic syndrome, the levels of serum visfatin were slightly higher when compared to subjects with T2DM without a comorbidity. The metabolic syndrome is made up of the collective presentation of multiple cardiovascular risk factors including abdominal obesity, hypertension, insulin resistance, hyperinsulinemia, and dyslipidaemia[37]. Increased macrophage expression caused by inflammation due to cardiovascular disease[36], along with the increase in visceral abdominal fat seen in obesity[7] could be causing the increase in levels of serum visfatin that is seen in subjects with T2DM with metabolic syndrome.

This meta-analysis updates the existing ones in the area by including studies published until 2020. Another strength of this study is that it accounts for heterogeneity through sub analysis of different factors such as age, gender, BMI, treatment modality, location of study, duration of T2DM, level of glycemic control and presence or absence of complications. This meta-analysis shows that the levels of serum visfatin are higher in subjects with T2DM when compared to their healthy counterparts. In addition, this study also shows that levels of serum visfatin are higher when a subject has a comorbidity that complicates T2DM.

The main limitation that was faced in this study was the presence of high heterogeneity which may be attributed to the observational studies used in this systematic review and meta-analysis whereby there may be differences in case-definitions, lack of confounder evaluation as well as differences in population settings, family history, ethnic backgrounds, lifestyle factors

and habits. Additionally, all studies included were of moderate quality and publication bias could not be excluded. Therefore, the findings need to be interpreted with caution.

This meta-analysis was performed as a step towards evaluating the potential of serum visfatin as a prognostic and diagnostic marker for T2DM. We found that levels of serum visfatin were increased in subjects with T2DM when compared to healthy adults, especially among those with comorbidities. However, since the findings have a high level of heterogeneity, they should be interpreted with caution. At this juncture, it may be premature to suggest that visfatin will complement existing means of DM control/diagnosis. We therefore recommend that future studies (1) employ a case-control design with matched confounders like underlying diseases, medication, treatment regimen and (2) use a prospective design to establish a cause–effect relationship between visfatin and T2DM.

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Conflict of Interest

The authors declare no conflicting interest.

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Original Article

The effect of a single dose of *Lactobacillus paracasei* strain *Shirota* on whole gut transit time among healthy young adults

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Introduction

Yakult contains *Lactobacillus casei* strain *Shirota (LcS)*. It has several protective effects on our digestive system which include preventing diarrhoea and improving constipation. The objective of our study was to determine the effect of a single dose of Yakult on whole gut transit time (WGTT) among young adults.

Methods

A cross-sectional study of 73 students who did not have any gastrointestinal disorder was performed. Subjects were given 4 carbon pills as a visual indicator to measure their WGTT in the normal setting of their usual activities. They then repeated measurement while consuming one dose of commercially available Yakult and 4 carbon pills (visual indicator). In the 2 settings, subjects were instructed to consume carbon pills and carbon pills with Yakult within 1 hour after bowel motion.

Results

The WGTT decreased in 48 of the 73 subjects (65.8%) after consuming Yakult. The mean WGTT was reduced by 4.4 ±14.6 hours. There was no significant effect of Yakult on the form of stools.

Conclusion

Yakult which contains *Lactobacillus casei* strain *Shirota (LcS)* is well known for helping in digestion and preventing constipation. A single dose of Yakult produces a reduction in the WGTT.

Keywords: *Lactobacillus casei* strain *Shirota (LcS), whole gut transit time (WGTT), bowel habit, constipation, factors affecting bowel habit*

INTRODUCTION

Yakult is a fermented skimmed milk drink containing a unique strain of bacteria, *'Lactobacillus casei Shirota' (LcS)* which reaches the gut alive.[1] In healthy individuals, gut microbiota maintains a symbiotic relationship with the gut mucosa. Beneficial bacteria in the digestive tract such as LcS serves to protect against toxic by-products of digestion. Studies have also shown that a normal gut microbiota has substantial metabolic, immunological and gut protective functions.[2] It is estimated that the gut microflora comprises of over 35,000 bacterial species.

The efficacy of probiotics has been clearly demonstrated in treating viral gastroenteritis and diarrhoea caused by antibiotics.[3] Both infection and antibiotics disrupt the natural balance of bacteria in the human digestive system, which probiotics can help restore. The other spectrum of digestive disorder, constipation, is however more common than diarrhoea. It affects about 14% of adults and accounts for about 3.2 million medical visits in the United States each year.[3] On average, Americans spend three-quarters of a billion dollars each year trying to ease their bowel opening. A study of 1,652 Malaysian students from Universiti Putra Malaysia showed that the prevalence of functional constipation among the students was 16.2%.[4] In a cross-sectional study of fruit consumption among Malaysian adults aged 20-39 by Universiti Kebangsaan Malaysia,

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it was found that the intake was 1.6±1.0 servings/day, which was lower than the Malaysian Dietary Guideline 2010 of >2 servings/day.[5] This may be the factor contributing to functional constipation.

Probiotics have been reported to relieve functional constipation, when it is measured by various outcomes such as symptoms, stool nature and frequency and gut transit time in a systematic review of randomized controlled trials.[6] Two out of 14 studies in a search of randomized controlled trials, one investigating the strain of *Bifidobacterium lactis* and another on *Lactobacillus casei Shirota*, showed a reduced whole gut transit time (WGTT) by 12.4 hours (95% CI 2.5 – 22.3).[6] The beneficial effects of probiotics may be explained by a few theories. One of it being that with increasing short fatty-acid chain production with ingestion of probiotics, the pH in the intestine will be reduced thus triggering peristalsis and consequently the WGTT.[7]

Normal WGTT or oro-fecal transit time, is considered to be between 10-73 hours. It consists of gastric emptying followed by transit through the small and large bowels. Studies show gastric emptying (GET) ranges from 2-5 hours, small bowel transit (SBTT) 2-6 hours and large bowel transit (CTT) 10-59 hours. GET, SBTT and CTT can be measured by a wireless motility capsule,[8] scintigraphy with radio-labelled markers or radiology with radio-opaque markers separately[9-10], but WGTT alone can easily be measured with ingestion of coloured or radiopaque markers[10-11] or dye[12] more easily.

LcS is a probiotic that has been found to improve functional constipation, including WGTT in several studies[7,13-15]. All these studies investigate long term use of LcS of at least 4 weeks. However, it is postulated that LcS may potentially benefit individuals even with administration of a single dose. This is because production of short chain fatty acids from fermentation of carbohydrates by these bacteria may happen immediately.[7,16]

Therefore, it is of interest to determine if ingestion of a single dose of Yakult culture drink (65ml) containing 6.5x 109CFU of LcS may affect WGTT and stool consistency in healthy young adults.

METHODOLOGY

Study design and setting

A cross-sectional study was carried out from August 2019 to December 2020 among undergraduate students enrolled in the medical programme in the International Medical University (IMU). The target population consisted of young adults without any gastrointestinal disease. Based on previous data whereby WGTT was measured using activated carbon as a marker, there was no significant change over several weeks, therefore the current study focuses on having the intervention group solely, without any controls.[17]

Ethical aspect

As this research required participants to consume Yakult and four activated charcoal tablets, verbal and written consent was obtained. Ethical approval was obtained from the International Medical University Committee on Ethics (CSc/Sem6(05)2020).

Inclusion and exclusion criteria

All students in the clinical campus without any gastrointestinal disease were invited to participate. Those who had been diagnosed with a colorectal, anal disease or on prebiotics or probiotic supplements, laxative and diarrhoea medication were excluded.

Individuals with comorbidities such as diabetes and hypertension were excluded. All participants were given clear information on the objectives, methods, possible risks and complications of this study. They were all required to sign consent forms before participating in this study.

Sample size and sampling

A sample size of 173 participants was required to detect a mean difference of 5% in the change expected in WGTT (i.e. 1.25 hrs, based on mean WGTT of 25 hrs) with 80% certainty (selectstatistic.co.uk).

Questionnaire and intervention

A structured questionnaire and data collection sheet was used as a survey instrument and sent to the participants via Google Form. Individuals were followed up to ensure that the participants understood the questionnaire to avoid misunderstanding and confusion. The questionnaire included the general information (name, age, gender, race, working status and medical condition particularly gastrointestinal disease), whole gut transit time (bowel habit, consistency of bowel movement, medication taken to help in passing motion), lifestyle (amount of water consumed in a day, amount of time spent in exercising in a week, stress level, meal time routine), beliefs (role of diet, amount of water and exercise in affecting the frequency of passing motion).

Participants were instructed on one occasion to consume only activated charcoal tablets within one hour of their bowel motion and record the time bowel motion occurred with the colour change subsequently. On the second occasion, they consumed both Yakult and activated charcoal tablets. They were asked to record the date and time of the first bowel motion, form of stools, time four tablets were taken, meal consumed on that day and the date where dark coloured stool was noted.

Statistical analysis

The data collected was entered into Microsoft Excel and exported into Statistical Package for Social Science (SPSS) version 26 for statistical analysis.

The duration of WGTT was non-parametric hence the Wilcoxon Signed Rank test was employed. Statistical analysis was done by using chi-square test for other categorial data. The statistically significant value was set as $p<0.05$.

Disclaimer

The funding for this research was provided by the IMU. Products (Yakult, charcoal tablets) used in this study were not sponsored.

RESULTS

In view of the restrictions we faced because of the Covid-19 pandemic, we were only able to enrol 73 subjects in the study which included 50 females and 23 males. The target subject of this study was young adults and the age of the subject recruited ranged from 19 to 27 years old. Most of the subjects are healthy students with no underlying comorbidities.

Forty eight out of 73 subjects (65.8%) had decreased WGTT after taking Yakult. On the other hand, 22 (30.1%) subjects had an increase in WGTT and 3 (4.1%) had no changes in WGTT after consuming Yakult.

The usual whole gut transit time of the subjects was considered short with 80.8% having <40 hours WGTT. The number increased in those with short WGTT with Yakult intervention (87.7%). However, the difference was not significant (p=0.249) (Table I).

Table I: Number & percentage of subjects having short (<40 hours) and long (≥40 hours) WGTT with carbon only vs carbon with Yakult.

Treatment	<40 hours WGTT	≥40 hours WGTT	P value
Carbon	59(80.8%)	14(19.2%)	
Carbon + Yakult	64(87.7%)	9 (12.3%)	0.249

There was a significant difference between WGTT with and without Yakult (p=0.012) as shown in Table II and Figure I.

Table II: Mean WGTT and difference in WGTT according to carbon only vs carbon with Yakult.

Measurements	Carbon only	Carbon + Yakult	P value
Mean (SD) WGTT (hours)	27.6 (14.3)	23.1 (11.7)	0.012
Difference in WGTT (hours)	-4.4 (14.6)		0.012

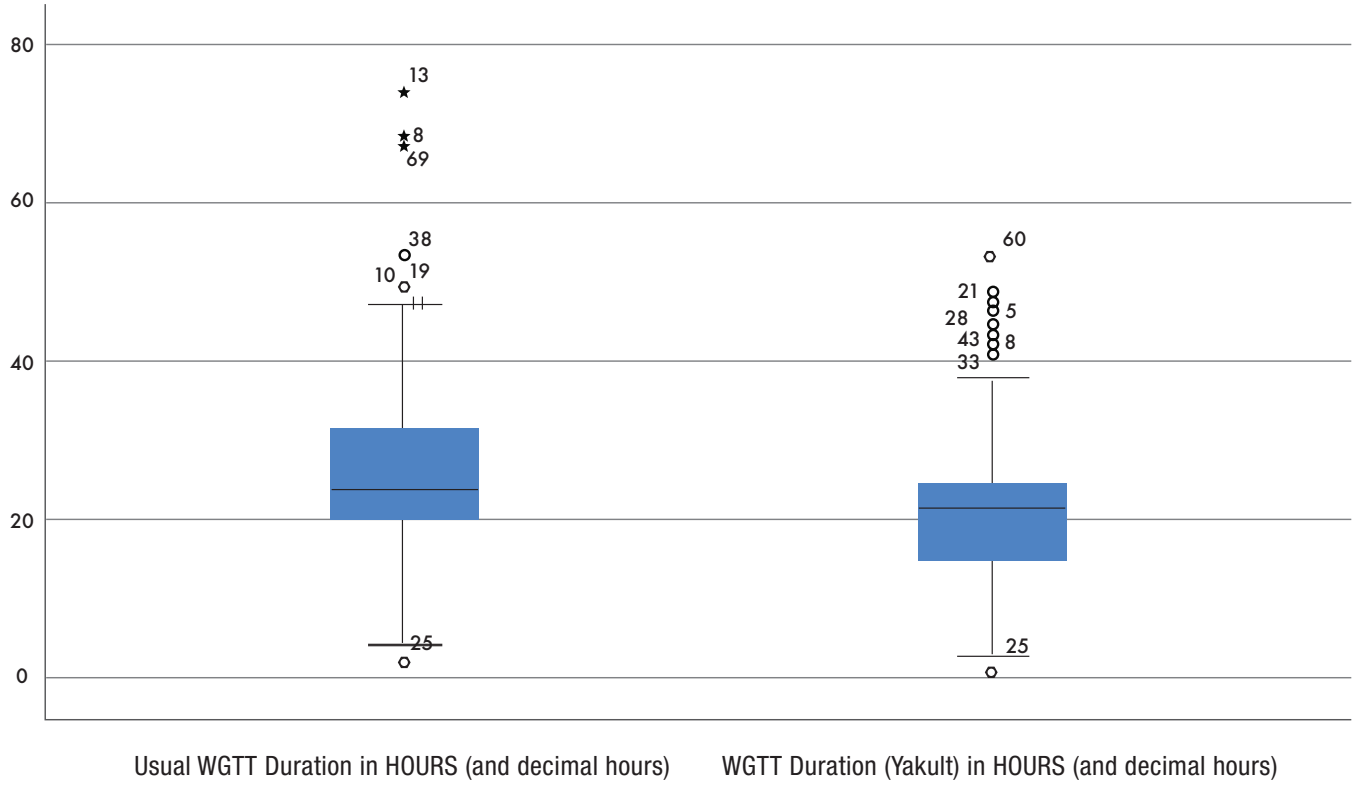

Figure I: Changes in WGTT with and without Yakult.

Treatment	Stool Type						
	1 (Pellets)	2	3	4	5	6	7 (Watery)
Carbon	1 (1.4%)	9 (12.3%)	21 (29%)	29 (40%)	8 (11%)	5 (6.8%)	0
Carbon + Yakult	1 (1.4%)	5 (6.8%)	17 (23%)	35 (48%)	6 (8.2%)	8 (11%)	1 (1.4%)

Table III: Bristol Stool Type before and after Yakult

There was a shift towards softer stool after taking Yakult *(LcS)* (Table III). The number of subjects with normal stool consistency (Types 3 & 4) increased from 69% -71% ($p<0.001$).

DISCUSSION

Based on the results, a single dose of Yakult shortens WGTT with a shift towards softer stool consistencies. Stool consistency is found to correlate with WGTT, with shorter WGTT producing softer stools.[18] Other studies on laxatives usually examine the effect of Yakult and other probiotics over a period of time and assess the effects using a questionnaire of bowel habits.[8] Medical opinion about the benefits of a single dose of probiotics as a laxative is ambiguous as probiotics are recommended on the basis of giving the bowel time to be colonized by the probiotic.

LIMITATIONS

Dietary differences may affect WGTT. We did not standardize the diet of the subjects prior to both WGTT measurements, but assumed that variations of diet among different individuals in a group will have no net difference in WGTT. Ideally, all participants should have been put on a standardized diet but having the subjects retain their habitual diet and lifestyle during the intervention phase, allows us to see the effect of single dose Yakult *(LcS)* in the real world.

Using activated carbon as an indicator poses the possibility it may affect WGTT itself. However, if it might, it is more likely to prolong WGTT.[19] Our measure of WGTT depended on the subjects reporting when they see a colour change and depended on the cooperation of the subjects. We cannot be sure that they identified the colour accurately and there are also occasions when stools drop into the water become unobservable, thus difficult to see.

The sample we obtained was smaller than we intended in view of the ongoing COVID-19 pandemic, thus it was difficult for us to recruit a larger sample size, and also investigate different age groups, which may yield more accurate results. Sample sizes are inversely proportional to margins of error – by having a smaller sample size, the margin of error is increased, and the confidence level of the study is also reduced. However, because the effect we obtained was larger than we expected, we saw a significant difference.

STRENGTHS

Our sample is largely homogenous. The population of students we sampled share many similar and common features in their environment, which controls for factors that may influence WGTT measurements, such as activities, lifestyle, and weather, which may influence hydration.

CONCLUSION

A single dose of *LcS* shortens whole gut transit time by 4.4 ±14.6 hours.

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Original Article

Association between pre-injury and injury-related factors and cognitive impairment of post-traumatic brain injury patients in a Hospital Universiti Sains Malaysia cohort

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Introduction: Traumatic brain injury (TBI) is one of the major global issues as it causes a serious health threatening condition for the injured persons, increased mortality rates, increased physical and cognitive impairment, as well as affecting the health care systems.

Method: The aim of this study was to predict the association between the pre-injury socio-demographic, injury-related factors and cognitive impairments in post-TBI patients. Self-administered questionnaires were used for descriptive correlational study. Three instruments used included (1) pre-injury socio-demographic characteristics (age, gender, race, religion, education level, occupation) (2) injury-related factor characteristics (location of brain injury and GCS) and (3) Montreal Cognitive Assessment (MoCA) questionnaire to estimate cognitive impairment.

Result: In this study, forty patients were recruited through purposive sampling from surgical based wards and 60.0% of TBI patients had cognitive impairments. This study found an association between injury factors (severity of TBI from GCS result) with cognitive impairment post-TBI among patients. However, there is no association between socio-demographic characteristics (age, gender, race, religion, education level, occupation) and cognitive impairment.

Conclusions: The study provided a better understanding on the association between pre-injury socio-demographic characteristics, injury related characteristics of the severity of TBI and cognitive impairments in post-TBI patients during hospitalisation. The results of this study can potentially be used as baseline information to improve the care and treatment needs of patients with cognitive impairment post-TBI during hospitalisation in relation to enhanced quality of life.

Keywords: *Traumatic brain injury, Pre-injury related factors, Injury related factors, Cognitive impairment post-TBI, Montreal Cognitive Assessment (MoCA).*

INTRODUCTION

Traumatic Brain Injury (TBI) is an acquired brain or head injury. It occurs when a sudden trauma damages the brain and disrupts normal brain function of the individual.[1] TBI is also known as an important medical, public health, and societal problem worldwide making it one of the leading causes of death and disability among children, adolescents, and adults.[2] TBI frequently occurs following motor vehicle-traffic crashes, impact or sport injuries, violence (gun and knife wounds) and falls, particularly in the elderly population. In addition, for those engaged in sports, mild TBI in the form of a concussion with or without loss of consciousness is a significant risk. While in military populations, blast-induced TBI has become the most common injury.[3]

Cognitive impairment following TBI is related to severity of TBI, location of brain injury, complications, concomitant injuries to other body regions, and chronicity of the injury.[4] Therefore, it is necessary to know how pre-injury (socio-demographic), injury related factors such as location of brain injury and severity of TBI could affect cognitive functions of TBI patients. Moreover, it is important to understand

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that cognitive impairment following TBI not only has profound effects on injured individuals but also their families, because long term disability makes the patients dependent on others.[5] Cognitive impairment caused by TBI also interferes with work, relationship, leisure, and activities of daily living, exacting a personal and economic cost that is difficult to quantify.[6] Therefore, understanding about the disease process following TBI will eventually help the injured individuals and families towards a positive recovery.

A previous study reported that males were at higher risk of TBI than females and the average age of TBI ranged from 27 to 58 years.[7] Therefore, studies on how socio-demographics (i.e. age, gender, races, religion, education and occupation) and injury related factors associated with cognitive impairment among TBI patients. This will help in a better understanding of post-TBI management, hence preventing this statistic from increasing by taking intensive prevention and precautionary steps.[4,6] Previous studies reported that there were relationships between demographic factors and cognitive impairment following TBI, for example the location of brain injury was found to be associated with effects on memory, attention, processing speed, and executive functioning of TBI patients and were mostly resolved within 3-6 months after injury.[4,6,7] A study also reported that severity of TBI associated with cognitive impairments, which found that moderate and severe TBI were associated with cognitive deficits, communication, visuospatial processing, intellectual ability, and awareness of deficit.[4] In addition, cognitive impairment following TBI was associated with location of brain lesion and severity of TBI. Therefore, this study aims to describe the association between demographic characteristics of injury related factors after TBI and risk of cognitive impairment by enhanced awareness among TBI patients and how their families sought early treatment and better care following TBI.

In addition, it is important to conduct this research because the nation needs to recognise that these injuries are preventable and are not the result of random events.[8] Besides that, there is a need to clarify groups at risk and risk factors to prevent TBI.[9] Since TBI patients require ongoing medical care, therefore good care management is required to ensure a better quality of life among post-TBI patients.[10] In summary, this study seeks to ensure that TBI patients can have good treatment and care in relation to enhanced quality of life post-TBI.

METHODOLOGY

Study design

A cross-sectional descriptive-correlational design was used in this study to determine the association between pre-injury socio-demographics, injury related factors and cognitive impairments of post traumatic brain injury patients in a Hospital Universiti Sains Malaysia cohort.

Sample and setting

This study was conducted at the surgical ward, Hospital Universiti Sains Malaysia (Hospital USM). Hospital USM is a sub-urban tertiary referral center for neurological disorders in the east coast of Peninsular Malaysia.

Sample size estimation and patients' recruitment

The participants of this study were TBI patients who were admitted to Hospital USM during data collection from February-March 2018. The inclusion criteria were male and female TBI patients who were hospitalised at surgical wards in Hospital USM, > 18 years old and who were conscious with mild (Glasgow Coma Scale

{GCS}: 13 – 15) to moderate (GCS: 9 – 12) GCS scores, were selected between days 5 to 14 following TBI. Meanwhile, the exclusion criteria included patients with severe neurological condition (GCS score: < 9), severe with other medical or mental illnesses. The estimation of sample was done using Raosoft calculation of sample size software based on the total admission of stroke patients per-year (2017) at Hospital USM. With the confidence level was 95% and margin error set at p < 0.05, the sample size recommended was 94. However, only forty patients were included in this analysis due to time limitations.

Pre-injury data collection

Pre-injury data included patient's socio-demographic characteristics including age, gender, race, religion, occupation, and education.

Injury related characteristics data

In this study, injury related characteristics data (severity of TBI score and location of brain injury) were collected. GCS was assessed during admission to determine the severity of TBI by measuring the patient's best eye responses, motor responses, and verbal responses. The score was classified as mild (GCS: 13 – 15), moderate (GCS: 9 – 12), and severe (GCS: < 9).[11] The location of the brain lesion was obtained from initial computed tomography (CT) scan report aided by an experienced radiologist. A Malay version of the Montreal Cognitive Assessment (MoCA)[12] was used to assess the level of cognitive impairment post-TBI in between after the patient gained full level of consciousness (GCS - 15) during in-patient setting. The agreement between BM MoCA and English MoCA was strong (intra-class correlation coefficient = 0.81, 95% CI 0.68-0.90).[12] MoCA is generally valid to measure the different cognitive domains (i.e. attention and concentration, executive functions, memory, language, visuo-constructional skills, conceptual thinking, calculations, and orientation) among study patients. The total possible score of MoCA are 0 to 30 points and a score of 26 or above is considered normal.[13]

Statistical analysis

The data were analysed using Statistical Package for Social Science (SPSS) version 24.0 (IBM Corp., Armonk, New York, USA). Alpha (α) was set at < 0.05 and for all analyses, $p < 0.05$ was considered statistically significant with confidence interval (CI) of 95%. Descriptive statistical analysis such as mean and standard deviation applied to all data. Frequency and percentage were applied to determine the pre-injury related factors (socio-demographic) and injury factors related to clinical characteristics (GCS, location of brain injury) among study patients. Chi-square analysis was used to identify the association between pre-injury (socio-demographic and injury factors (GCS, location of brain injury) and cognitive impairments in post-TBI patients.

Ethical consideration

Ethics approval was obtained from the Human Research Ethics Committee - Universiti Sains Malaysia (JEPeM-USM).

RESULTS:

Pre-injury socio-demographic profiles

A total of 40 patients, aged between 18 to 80 years (mean age: 34.18 ± 15.39) with TBI were recruited. Whereby, 18 (45%) of them were within 18 – 25 years of age, followed by 12 (30%) patients from 25 – 36 years. The lowest number of patients (4) were in the age group

36 – 45 years (10.0%). In this study, the total number of patients were mainly males (92.5%), Malay and Muslim (95%), employed (62.5%), and with higher education (92.5%). Table I summarises the frequency distribution of pre-injury socio-demographic profiles among the study patients.

Table I: Frequency, percentage and association between socio-demographics and post-injury cognitive impairments among TBI patients in Hospital USM

Socio-demographic	Frequency	Percentage %	Cognitive dysfunctions, n (%)		*p* value
			Normal	Dysfunctions	
Age					**.33**
18-25	18	45.0	8 (20.0)	10 (25.0)	
26-35	12	30.0	3 (7.5)	9 (22.5)	
36-45	4	10.0	1 (2.5)	3 (7.5)	
46-80	6	15.0	4 (10.0)	2 (5.0)	
Gender					**.26**
Male	37	92.5	16 (40.0)	21 (52.5)	
Female	3	7.5	0 (0.0)	3 (7.5)	
Race					**.51**
Malay	38	95.0	16 (40.0)	22 (55.0)	
Chinese	2	5.0	0 (0.0)	2 (5.0)	
Religion					**.51**
Islam	38	95.0	16 (40.0)	22 (55.0)	
Buddha	2	5.0	0 (0.0)	2 (5.0)	
Education Level					**1.00**
High Education	37	92.5	15 (37.5)	22 (55.0)	
Low Education	3	7.5	1 (2.5)	2 (5.0)	
Occupation					.74
Employed	25	62.5	11 (27.5)	14 (35.0)	
Unemployed	15	37.5	5 (12.5)	10 (25.0)	

* In all analyses, *p*-value of <.05 was considered as significant, all null hypothesis will be rejected.

Injury factors characteristics

This study found that 24 (60%) patients (mean age: 28.96 ± 12.15) had brain lesions at more than one cerebral region. Whereas, nine (22.5%) patients (mean age: 34.11 ± 14.99) had a brain lesion in the frontal lobe of the brain and one (2.5%) had a lesion in the occipital lobe. In terms of severity of TBI, this study found that 23 (57.5%) of the patients (mean age: 31.78 ± 13.31) fell in the mild GCS category and 17 (42.5%) patients (mean age: 31.94 ± 14.733) were in the moderate GCS category (Table II).

Table II: Frequency and percentage of clinical characteristics of participants (n=40)

Characteristics	Frequency	Percentage (%)
Location of brain injury		
Frontal lobe	9	22.5
Parietal lobe	3	7.5
Occipital lobe	1	2.5
Temporal lobe	3	7.5
Combination	24	60.0
GCS		
Mild	23	57.5
Moderate	17	42.5

Cognitive impairments post-TBI score using the Montreal Cognitive Assessment (MoCA)

The cognitive impairment post-TBI score was determined using the Bahasa Malaysia Montreal Cognitive Assessment (MoCA). The Cronbach alpha value for MoCA questionnaire for this study was tested and the result was 0.74, indicating that this questionnaire was valid and reliable. The analysis of cognitive impairments post-TBI found that the mean and standard deviations of the executive category was 2.58 ±1.99, attention category was 5.23 ± 0.70, language was 2.90 ± 0.30, abstraction was 1.58 ± 0.55, recall memory was 4.00 ± 1.01 and lastly orientation was 6.00 ± 1.48. The cognitive impairments post-TBI variables of MOCA were then classified into Cognitive Impairment post-TBI and Normal Cognitive Function post-TBI. The results revealed that 24 (60.0%) participants (mean age: 32.08 ± 13.33) had Cognitive Impairment post-TBI whereas only 16 (40.0%) participants (mean age: 31.50 ± 14.79) were in the Normal Cognitive Function post-TBI category.

Association between pre-injury socio-demographic, injury related factors and cognitive impairments post-TBI in Hospital USM patients.

The results revealed that there was no significant association between pre-socio-demographic and cognitive impairment post-TBI (MoCA) (Table I). However, there is a significant association between severity of TBI (GCS) and cognitive impairments post-TBI (MoCA) ($p > 0.05$) (Table III). There was no association between location of brain injury and cognitive impairments post-TBI (MoCA) ($p > 0.05$).

Table III: Association between clinical characteristics for GCS and post-injury cognitive impairments

Clinical Characteristics	Cognitive impairments n (%)		*p* value
	Normal	Impairment	
GCS			.01
Mild	13 (32.5)	10 (25.0)	
Moderate	3 (7.0)	14 (35.0)	

Impairment among TBI patients in Hospital USM

* In all analyses, p-value of <.05 was considered as significant, all null hypothesis will be rejected.

DISCUSSION

Association between socio-demographic characteristics, injury related factors and cognitive impairments Post-TBI in Hospital USM patients

This study successfully recruited 40 patients with TBI in the Neuro Unit at Hospital USM. Based on this study, the highest group of participants (45.0%) were in between the ages 18-25 years, followed by the groups aged between 26-35 years (30.0%), and between 46-80 years (15.0%); the lowest was 36-45 years (10.0%). A previous study reported that higher incident rates for TBI were among those age between 15-25 years old (31.7%), followed by those between 26-35 years (22.5%), and the lowest was amongst the ages 36-45 years (19.5%).[10] However, there was no significant association between age and post injury cognitive impairment. It means that age group is not associated with post injury cognitive impairment.

In terms of gender, the majority (92.5%) of the participants were male whilst 7.5% were female. Majority of the male TBI patients were diagnosed as due to motor vehicle accident, however some of them were due to falls or assaulted with sharp objects. Other study also showed that the majority of participants were males (97.5%)[14] and 55.0-66.0% of male participants were diagnosed with TBI due to motor vehicle accident.[15-16] However, there was no significant association between gender and post injury cognitive impairment. It means that gender is not associated with post injury cognitive impairment, as majority of previous studies had mixed results on the gender association with post injury cognitive impairment[17] and it is not gender specific.[18]

Furthermore, participants in this study showed that majority (92.5%) had adequate education. Other studies also reported that TBI patients (62.0%) had adequate education.[15] Besides that, through this study it could be explained that the majority of TBI patients were employed (62.5%) compared to unemployed (37.5%). A previous study identified that 81.0% of TBI patients were employed.[19] It was important to know about education level and occupation among TBI patients because either being employed or unemployed and having adequate education level at the time of injury is not related to post injury cognitive impairment post-TBI.[20]

In addition, this study found no significant association between socio- demographics and post injury cognitive impairments. Previous study also reported that there is no significant association in occupation[21], level of education[22], gender and age.[9]

Therefore, the findings of this study and previous study results could explain that socio-demographics would not affect participants with post-TBI cognitive impairments. Although one longitudinal study (10-years follow-up)[15] had argued that participants with less education had performed poorly in post-TBI cognitive assessment. Therefore, a follow-up study needs to be done to further elucidate the outcome from our study.

Association between injury factors related to clinical characteristics and cognitive impairments post-TBI in Hospital USM patients

This study explained that the clinical characteristics involved were severity of TBI using GCS and location of brain injury. In this study, mild GCS had the highest frequency with 23 (57.5%) while moderate GCS had 17 (42.5%). Besides that, severe GCS was excluded as stated in exclusion criteria. In addition, it was important to describe that mild severity of TBI was significantly associated with negative effect or disruption on physical, emotion and cognition.[10] Furthermore, other studies also found that mild GCS (n=31), moderate GCS (n=12) and severe GCS (n=8) may contribute to post cognitive impairment.[11]

Next, this study found an association between clinical characteristics of GCS and cognitive impairments among traumatic brain injury patients at Hospital USM. Up to 35.0% of moderate (GCS = 14) and mild (GCS = 10) had cognitive impairments. Previous study also explained the significant association of severity of TBI with cognitive impairments.[24] Besides that, it was also stated that persistent symptoms even from mild GCS could be associated with long-term impairment in areas such as cognitive functions.[14] Therefore, GCS is an important clinical characteristic because it was stated about TBI severity leads towards cognitive impairments as shown in this study.

In comparison, moderate-to-severe TBI is associated with significant impairments in sensorimotor, cognitive, and psychosocial functioning. Cognitive impairments include problems with executive functioning, memory, and attention, which is reduced capacity for new learning and decreased speed of information processing.[6] While deficits typically improve spontaneously in the early months after injury, most patients with moderate-to-severe injury have lifelong challenges that have a tremendous influence on everyday independence, work, and social life.[25] Moreover, cognitive impairments due to moderate and severe TBI effects are particularly prominent in terms of information processing, speed and attention, memory and executive functioning.[6]

The results revealed that 60.0% of TBI patients experienced more than one location of brain injury. While injury in the frontal lobe of brain (22.5%) and parietal lobe and temporal lobe (7.5%) of brain should be given high consideration because injury in these locations contribute to post injury cognitive impairment. However, no significant association between clinical characteristics for location of brain injury and cognitive impairments were found among traumatic brain injury patients at Hospital USM may be due to small sample size.

This suggestion is supported by findings of another study whereby majority of TBI cases had brain

injury at the frontal lobe (33.4%) and had cognitive impairment.[23] This study also showed that participants had more cognitive impairment due to combination brain injury (40.0%) compared to only frontal lobe (10.0%) and temporal lobe (7.5%). In contrast, there was a study finding that reported significant associations between cognitive impairments and frontal lobe brain injury which resulted in impairments of verbal episodic memory (delayed recall and recognition) but presented normal performance on visuospatial episodic memory (recognition), short- term memory and non-verbal skills.[23]

Given the high prevalence of executive deficits in TBI patients, it is not surprising that the frontal lobes and their related circuitry (subcortical white matter, basal ganglia, and thalamus) are particularly vulnerable to TBI. Working memory and planning deficits may be associated with the focal injury to the dorsolateral prefrontal cortex affecting the projections between the lateral frontal and posterior regions. Apathy has been associated with subcortical lesions and right hemisphere dysfunction. Impaired awareness is characteristic of patients with focal frontal injury, and the post-injury level of self-referential insight has been associated with the integrity of right dorsal prefrontal cortex. Decision-making is a complex cognitive function and correlates to its component skills in patients with moderate to severe TBI. Deficits in risk adjustment were associated with abnormalities in subcortical structures such as the thalamus, the dorsal striatum and the caudate. Impulsivity was associated with abnormal diffusion tensor imaging findings in the bilateral orbital frontal gyri, insula, and caudate whereas impaired rational choice related to changes in the bilateral dorsolateral prefrontal cortex, the superior frontal gyri, and the right and ventromedial prefrontal cortex, ventral striatum, and hippocampus. This pattern of results suggests that the emotional components of decision-making will risk adjustment and impulse control; predominantly involve subcortical structures and the interplay between frontal and subcortical systems. Then, cognitive components of decision -making, such as rational choice, rely heavily on the prefrontal cortex.[4]

Strength and limitations

The main strength of this study is of the related factors such as socio-demographic and clinical characteristics that contribute to cognitive impairments due to TBI. In addition, Cronbach alpha for MoCA questionnaire at 0.74 indicated that this questionnaire was valid and reliable. Thus, it provided a good and reliable measuring tool for assessing cognitive impairments. Although this research was carefully prepared, the researchers were still aware of its limitations and shortcomings. The limitations of this study were mainly due to small sample size and follow-up sessions needed.

Implications and recommendations

This finding has essential implication to health care providers of TBI patients. The healthcare providers especially medical doctors and nurses have an important role in ensuring TBI patients' access to quality care and treatment management to ensure a better quality of life post-TBI. Besides that, the information from this study will help nurses and other healthcare providers become more prepared to care for TBI patients and participate more to ensure that the patients could recover and return to their daily life. Care of TBI patients with cognitive impairment post-TBI requires long term rehabilitation to achieve better cognitive and physical functioning in relation to gaining high quality of life post-TBI.

The study presents better understanding on the association between pre injury socio-demographics, injury related characteristics and cognitive impairments among post-TBI patients at Hospital USM. However, further studies are strongly recommended. Hence, further research should include a larger number of participants and assessment on the severe level of GCS. The design of this study can be used in further advanced research to achieve a high significant result and hencean increased number of samples is recommended.

CONCLUSION

This study was aimed to analyse, identify the pre-injury, injury related to clinical characteristics, and cognitive impairments among post-TBI patients at Hospital USM. Therefore, more than half of the participants were found to have post injury cognitive impairments due to TBI. In this study, the researchers identified that there were no association between pre-injury socio-demographics, injury related characteristics (location of brain injury) and cognitive impairments among post-TBI patients at Hospital USM. The analysis revealed that there were associations between clinical characteristics of severity of TBI using GCS and cognitive impairments among TBI patients at Hospital USM. Limited understanding about TBI patient health condition could contribute towards poor care and treatment for them. Therefore, having adequate understanding about their health conditions could help healthcare providers especially medical doctors and nurses become more prepared in giving the best care and participating in TBI patient recovery process.

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AUTHOR CONTRIBUTION STATEMENT

NMR contributed to the entire part of the research and manuscript preparation.

MNCMY contributed to manuscript preparation **SH** contributed to study conception, funding, supervision and manuscript preparation.

DISCLOSURE / CONFLICT OF INTEREST

The author(s) declare no potential conflicts of interest with respect to the research, authorship and/or publication of this article.

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Original Article

24-hour observation of patients after intrathecal morphine for lower segment caesarean section – Is it overrated? A prospective observational study

Thiruselvi Subramaniam, Shu Ning Kong, Shi Ting Tee, Muhammad Faiz Bin Ismail, Joanne Sue James, Hamitra Gandhi

Background: Side effects of intra-thecal (IT) morphine in lower caesarean section (LSCS) can be dangerous hence they are co-managed by the anesthesia pain team for a minimum of 24 hours. The aim of this study was to identify the side effects and consider the possibility of earlier discharge from the pain team to the parent team.

Methods: A prospective observational study was conducted on 323 patients who received IT morphine for LSCS. An interviewer-centered questionnaire was used to obtain data on the side effects.

Results: Side effects were experienced by 80% (n=259) of the patients, and none developed respiratory depression. Side effects occurred in first 6 hours in 94%(n=244) of the patients, 5% (n=13) within 6 to 12 hours and 1% (n=2) within 12 to 24 hours. Pruritus was the most common side effect (88%; n=227) and 93% (n=210) experienced it within the first 6 hours. Nausea and vomiting occurred in 54% (n=139) of the patients with side effects and 70% (n=97) of them experienced them within the first 6 hours. Kruskal-Wallis H test showed that Malays experienced more side effects, $\chi^2(2) = 3.363$, $p = 0.004$. No difference in pain scores was noted between races at 0-6 hours and 12-24 hours. However, Indians had higher scores at 6-12 hours ($\chi^2(1) = 4.31$, $p = 0.031$).

Conclusion: The most common side effect was pruritus, then nausea and vomiting with no respiratory depression. Most occurred in the first 12 hours suggesting possibility of earlier discharge by the pain team to the parent team. However, further research is needed as guidelines suggest 24 hours, fearing respiratory depression. Side effects in Malays and increased pain perception among Indians need exploration.

Keywords: *Caesarean Sections, Drug side effects, Intrathecal morphine, Race, Respiratory depression.*

Background

Neuraxial opioid refers to the epidural or intra-thecal administration of opioids. Intra-thecal and epidural opioids have today become part of a routine process for the management of post-operative pain. Intrathecal use of opioid for pain relief was reported as early as the 1900s in Romania and Japan and after a void it became increasingly used after Wang et al reported the treatment of cancer pain with intra-thecal morphine in 1979.[1, 2]

Intrathecal morphine (IT morphine) has been proven to improve the management of pain post- lower segment caesarean sections (LSCS) and other surgical procedures.[3-8] However, side effects of morphine can be dangerous and distressing to patients and clinicians, especially pruritus, nausea, vomiting, and respiratory depression.[9,10] The dreaded respiratory depression is the main reason why patients after IT morphine are followed up for up to 24 hours. According to the practice guidelines by the task force on neuraxial opioids, the American Society of Anesthesiologists and American Society of Regional Anesthesia and Pain Medicine, respiratory depression may be indicated by: (1) reduced respiratory rate to less than 10 breaths/min, (2) reduced oxygen saturation or (3) hypercapnia/hypercarbia. The guidelines also suggest other measures of respiratory

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function like tidal volume or clinical signs such as drowsiness, sedation, periodic apnea, and cyanosis as indicators of respiratory depression.[11-13]

The practice by the Acute Pain Service (APS) team at our hospital is to follow up all post-LSCS patients who received intra-thecal morphine for the first 24 hours. This is to identify, prevent or manage life-threatening conditions like respiratory depression, other common side effects like pruritus nausea and vomiting. The question raised was, if the follow up duration of the IT morphine patients can be reduced, patients can then be discharged to parent team sooner for further continued management. Hence, we aimed to identify the side effects of IT morphine at 0-6 hours, 6-12 hours, or 12-24 hours after administration for LSCS. A minor objective was to also compare side effects among different races, considering the racial diversity of the patients in our hospital.

Methods

This is a prospective observational study conducted in the post-natal ward of a tertiary public hospital on patients (18 to 45 years of age) who were administered IT morphine during the induction of spinal anesthesia for the management of post-LSCS pain. A sample size of 384 was calculated based on a population size of 1000000, confidence interval of 5 and confidence level of 95%. However, we were able to recruit a total of only 323 patients in the time period of 6 months that we had for data collection. Patients who consented, signed a consent form agreeing to participate in the study and were informed that all information will be kept confidential. The study information was provided to all patients in a written form and verbal explanation was also provided.

Patients between the ages of 18-45 undergoing LSCS, who had no contraindication for spinal anesthesia and who received IT morphine, were included in the study. Patients who were excluded were those – 1) who refused participation, 2) had combined spinal epidural (having a catheter inserted epidurally for post-op pain, 3) had spinal anaesthesia without IT morphine, 4) morbid obesity, 5) allergy to morphine. An interviewer-centered questionnaire was used to obtain demographic information from patients. The questionnaire included demographics such as age, race and previous history of lower segment caesarean section with spinal anaesthesia, time to ambulation, the presence of pain over the incisional site, the presence of intrathecal morphine side effects and the sedation score.

The intrathecal cocktail used for lower section caesarean surgery was hyperbaric bupivacaine 12mg, fentanyl 10ug and 0.1mg morphine. Patients were monitored closely in the wards as per requirement of all post-operative patients but these group of patients had close monitoring of respiration and state of sedation as they had received IT morphine for their surgery. Post-operative evaluation of the patients for the research, however, was carried out at intervals of 0-6 hours, 6-12 hours and 12-24 hours using the questionnaire and was completed by patients with the assistance of the investigator. This time interval was chosen as it was convenient for the investigators and their availability to assess the patients, as well as to avoid frequent interruption and disruption of patients' post-operative recovery period. The targeted side effects were pruritus, sedation, nausea, vomiting and respiratory depression.

Pain score was assessed using modified Wong-Baker FACES Pain Rating Scale and pruritus was assessed using a score modified from the Wong-Baker visual pain score. Based on the protocol used in the hospital, respiratory depression was defined as respiratory rate of less than 8 breaths per minute. Sedation was assessed using the scoring system used routinely in the hospital.

Side effects targeted

a) Pruritus

Pruritus was categorised into localised pruritus and generalised pruritus. Localised pruritus meant a single area of itchiness and generalised pruritus meant more than one region of itchiness. The degree of pruritus was assessed as mentioned earlier, a score modified from the Wong-Baker visual pain score and pruritus intensity assessment questionnaire.

0 = no itch

2 = itch relieved by gentle rubbing

4 = itch relieved by scratching

6 = itch unrelieved by scratching

8 = itch unrelieved by scratching with excoriation

10 = itch affecting sleep

b) Respiratory depression

Respiratory rate of less than 8 breaths per minute was considered as respiratory depression.

c) Sedation

Sedation score was evaluated using the sedation score by the hospital, where 0 = none (patient is awake/ alert), 1 = mild (occasionally drowsy), 2 = moderate (frequently drowsy, easily roused), 3 = severe (difficult to rouse) and S = sleeping (easy to rouse).

d) Nausea and vomiting

Data analysis and Ethical clearance:

The data collected was analysed using SPSS and the statistical analysis was carried out using the Chi square test and Kruskal Willis test with statistical significance set at $p < 0.05$.

Ethical clearance was obtained from the International Medical University Ethical Joint Committee of Research and Ethics; ID No: CSc / Sem6(17)2015 and the National Malaysian Medical Research ethical committee.

Results

Patients' ages ranged from 18 to 43 with a mean of 30.3 years (SD=5.32) and they were categorised into three groups; 1) less than 29 years old (46%; n=149) 2) 30-39 years old (50%; n=160) and 3) more than 40 years old (4%; n=14). Most patients who had side effects were of ages between 30-39 years (80%; n=130). However, there was no statistically significant association between age group and the presence of side effects, $\chi^2(2) = 0.229a$, $p = 0.892$.

Of the 323 patients, 65% (n=209) were Malay, 10% (n=32) Chinese, 20% (n=65) Indian and 5% (n=17) were of other races which included the aboriginals and foreigners. Our study results show that 9% (n=29) of the patients began ambulating within 6 to 12 hours, 83% (n=269) by 12 to 24 hours and 8% (n=25) did not ambulate after 24 hours because they still had urinary catheters in-situ due to other obstetrical reasons. We found that 80% (n=259) of the patients experienced at least one side effect of IT morphine at some point in time during the post-operative review and 20% (n=64) did not experience any side effects at all (Fig. I). However, no patient developed respiratory depression. (Fig. II)

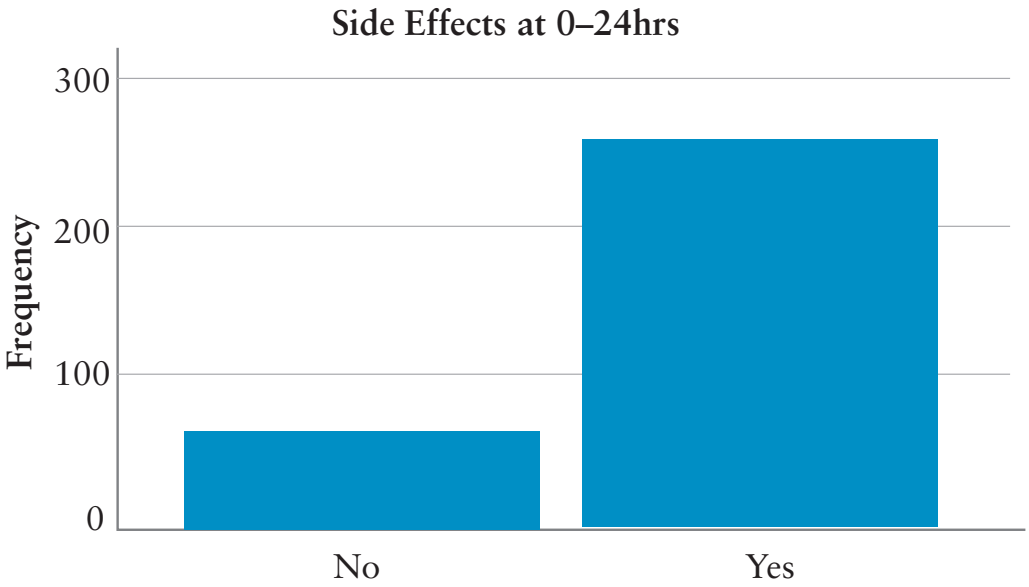

Figure I: Appearance of side effects in the first 24 hours

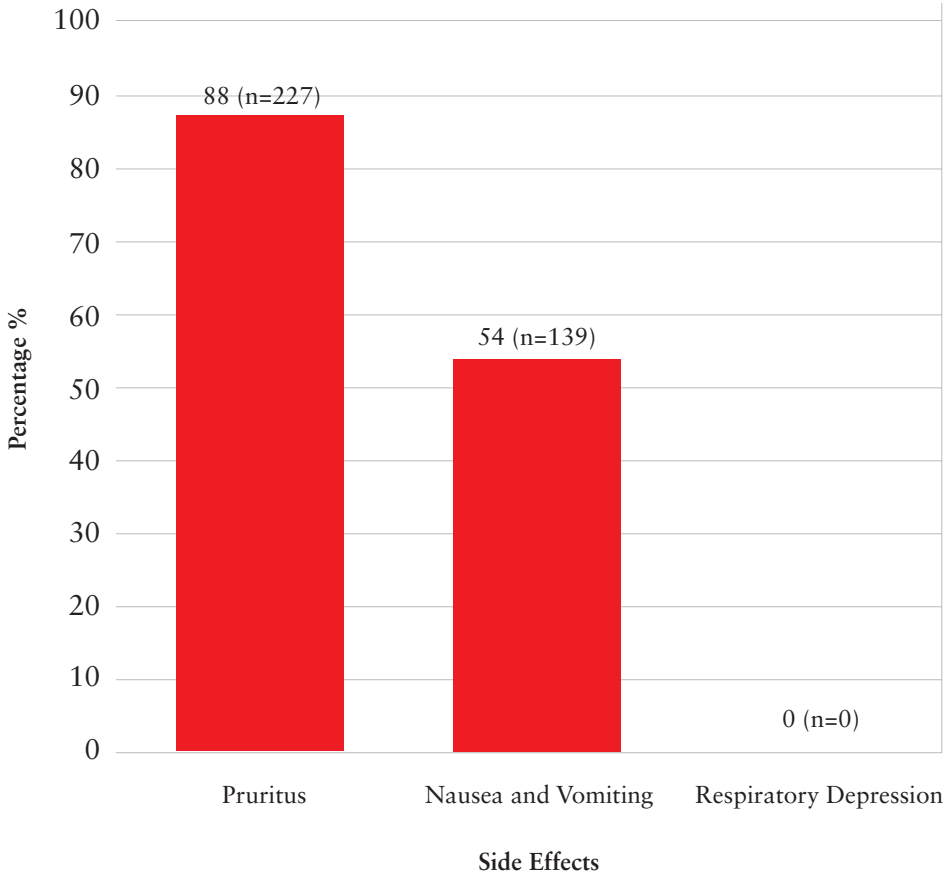

Figure II: The most common type of side effects identified in patients who developed side effects (n=259)

Kruskal-Wallis H test showed a statistically significant difference in side effects between the different races, $\chi^2(2) = 3.363$, $p = 0.004$, with a mean rank side effect of 170.05 for Malays, 148.58 for Chinese, 139.34 for Indians and 175 for Others. Interestingly we found that the Malay population experienced more side effects than the Chinese and Indians.

Side effects commonly occurred within the first 6 hours, as apparent in 94%(n=244) of the patients, 5% (n=13) within 6 to 12 hours and 1% (n=2) within 12 to 24 hours. (Fig. III) Pruritus was the most common side effect (88%; n=227) and majority (93%, n=210) of the patients experienced it within the first 6 hours. Among the Malays with side effects, pruritus appears to be the most common (90%; n=160).

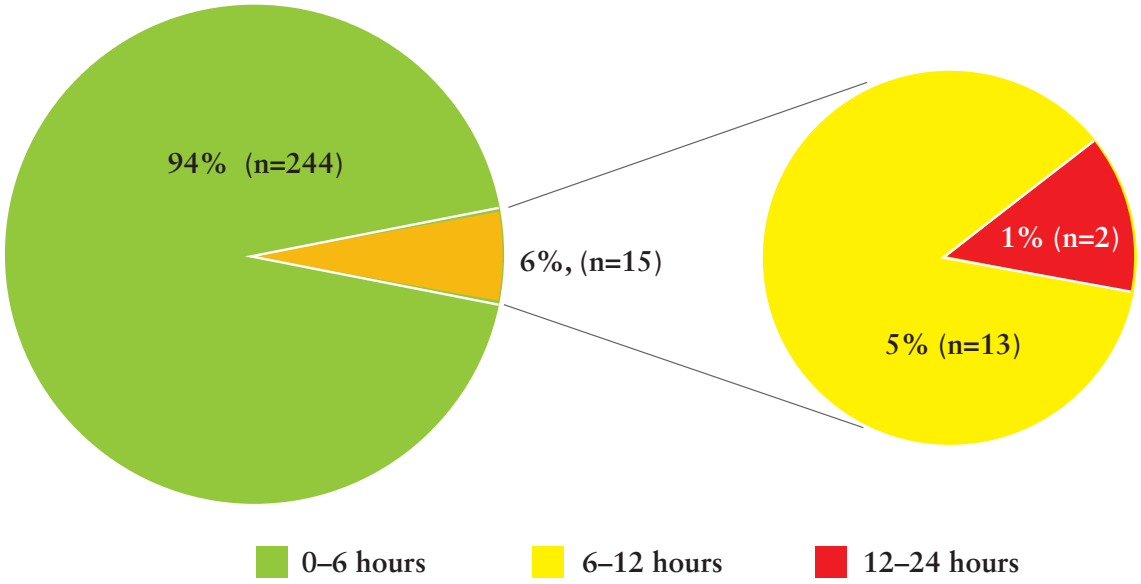

Figure III. Relationship of the onset of side effects and time

Of the total 210 patients with pruritus in the first 6 hours, 43% (n=90) had localised pruritus and 57% (n=120) had generalised pruritus. However, some (10%; n = 9) of the patients with localised pruritus in the first 6 hours eventually developed generalised pruritus. Of the 227 patients, the face was the most common location of pruritus (82%; n=186). Nausea and vomiting occurred in 54% (n=139) of the patients who had side effects and 70% (n=97) of them experienced this within the first 6 hours.

Pain

The mean pain score of the patients was the lowest during the first 6 hours (1.9 ± 2.1) and progressively increased in the 6-12-hour period (2.1 ± 2.0) and the 12-24-hour period (2.5 ± 1.9). However, the scores were generally within acceptable range. There was no difference in pain scores among the different races during the 0-6 hours, $\chi^2(1) = 1.39$, $p = 0.239$) and 12-24 $\chi^2(1) = 2.88$, $p = 0.090$) hours post IT morphine.

However, Indians had higher scores at 6-12 hours. $\chi^2(1) = 4.31$, $p = 0.031$) compared to the other races (Malays, Chinese and Others).

Sedation

None of the patients had a sedation score of more than 2 (drowsy but rousable), 63% (n=204) had a sedation score of 1 (occasionally drowsy-mild) and the rest, 37% (n=119) has either a score of 0 or S (sleeping). It was noted that that 97% (n=197) of those who were mildly sedated were so in the first 6 hours.

Discussion

Most of the side effects caused by IT morphine occurred within the first 12 hours of administration in our study. Nausea/vomiting was the second common side effect (54%; n-139) noted in our population of patients usually occurring in the first 6 hours, pruritus being the most common (88%; n=227). These findings were similar to other studies.[3, 14] Most studies identify pruritus, nausea, vomiting and urinary retention as common side effects of IT morphine though there appear to be inconsistencies regarding incidence of the most feared respiratory depression. The varied definitions about respiratory depression (respiratory rate of less than 8 or less than 10) could perhaps contribute to the inconsistencies in results from the various studies.[10, 12, 13, 15, 16]

This dose of morphine used at our premise is 0.1mg combined with fentanyl and bupivacaine. The dose of 0.1mg IT morphine is identified as optimal with minimal side effects for LSCS as evidenced in several research.[3, 10, 17, 18] Higher doses of IT morphine are known to provide adequate pain relief but at the expense of more side effects. The IT dose of 0.1mg morphine given intrathecally is found to have lesser side effects but with similar pain relief compared to higher doses.[4, 10, 19, 20, 21]

There have been debates about ethnicity and pain. Most studies on ethnicity and perception of pain are centered around the western population. A systematic review and meta-analysis by Kim et al found that Asians and Hispanics had higher pain sensitivity compared with non-Hispanic whites.[22] However, a study on perception to thermal pain among Indians, Chinese and Malays did not show any significance between the three groups. This could be because of the setting of the studies which were quite different and conducted in a controlled environment.[23] Knowledge about perception of pain among the different races will help in the improvement of post-IT morphine pain management. Earlier, routine administration of other form of pain medications would improve post-operative outcomes for the respective group of patients.

Our findings however, showed that, though there were no differences in pain scores in the 0-6 and 12-24 hours post IT morphine, there was significant difference in the 6-12 hour period, with Indians having higher scores (≥ 4 on the Wong- Baker's FACES Pain rating scale) compared to the other races (Malay, Chinese and Others) at 6-12 hours, $\chi^2(1) = 4.31$, $p = 0.031$). A study conducted on ethnic differences in pain perception and patient controlled analgesia usage post-LSCS where intrathecal morphine was used along with local anaesthetic had similar results.[24] A quantitative review of ethnic group differences in experimental pain response suggested that there are potentially important ethnic/racial group differences in the perception of pain. Demonstrating ethnic group differences, they felt would transfer to a more culturally competent clinical care. It would address and reduce pain treatment disparities among ethnically/racially diverse groups.[25] Furthermore, explorations into relevant psychological and socio-cultural factors may reveal more information

with regards to the relationship of pain perception and ethnicity.[23, 24, 25, 26, 27] The sample size in our study was a limitation that can be remedied in future by conducting a more focused research on perception of pain among these three major ethnic groups in our country.

The incidence of pruritus is 83% in postpartum patients and 69% in non-pregnant patients including males and females.[28, 29] Pruritus can cause significant discomfort to patients who receive IT morphine. Incidence of pruritus is noted to be related to higher doses of IT morphine. In our study pruritus appears to be a more common side effect than others like nausea and vomiting though we used relatively lower doses of morphine intrathecally. There are other studies that identify pruritus as a more common side effect in patients receiving intra-thecal opioids.[4] Mechanism of intrathecal opioid-induced pruritus is complex and the literature data on the pathogenesis is still not clear though there have been many discoveries and explanations to the cause.[30] Distribution of pruritus has been noted to be mainly in the upper half of the body, though in some cases it maybe generalised. In our case we found that most patients had pruritus on the face compared to other parts of the body.

Respiratory depression is one of the most dreaded side effects of intrathecal opioids. Swart et al reported 0.02% (n=1) incidence of respiratory depression (respiratory rate <10) in a study conducted on 60 patients who underwent LSCS with 0.1mg IT morphine.[3] In our study none of the patients developed respiratory depression, findings being similar to a retrospective study by Crowgey et al in 5036 obstetric patients.[31] However, the absence of respiratory depression does not imply the absence of this feared side effect in view of our sample size and thus may require further research. It is believed that the lack of a universally accepted definition and the variability of the IT doses used have prevented us from establishing the true incidence of respiratory depression.[12] A meta-analysis on side effects of morphine showed that the risk of respiratory depression seems not to be increased in patients receiving IT morphine < 0.3mg compared to placebo suggesting that using lower doses would provide a bigger safety margin with respiratory depression. In the obstetric patients, the higher levels of progesterone, a potent respiratory stimulant, makes it safer to use the neuraxial opioids. [12, 13, 31]

Conclusion

The results of our research suggest that 12-hour monitoring by APS team is adequate before discharging from the APS care and regular monitoring can be continued in the ward by the parent team. This will help in the redistribution of workload for the APS team and useful time management.

Further study with a bigger sample size may be needed to look at the predominance of side effects that were noted among Malays compared to the Chinese and Indian population in our study and reaffirm that respiratory depression is not the most dreaded side effect at low doses. Our study suggests that Indian women have a lower threshold for perception of pain, and it would be interesting to re-look at the racial differences using a bigger sample size.

Limitations

- The sample size was limited also by the duration available for the research.
- A bigger sample size would be required identify the significance of racial differences in perception of pain.

Conflict of interest and funding

There is no conflict of interest for the conduct of this study. No funding was needed.

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Original Article

Cross-cultural adaptation of the General Functioning Scale of the family into the Malay language

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Introduction: The McMaster Family Assessment Device (FAD) has been used to measure family functioning in several cultures. The FAD's 12-item General Functioning Subscale (GF12) provides a general assessment of family functioning. This study aims to assess the cross-cultural adaptation of the FAD-GF12 scale in the Malaysian population.

Methods: The translation and adaptation procedure of the Malay GF12 was based on the dual-panel methodology. This involved a bilingual panel (providing the initial translation into the Malay language) followed by a lay panel (where items are assessed for comprehension and acceptability). A mixed-methods approach with exploratory sequential study design was employed. This study used a mixed-methods approach, combining a quantitative survey of the Malay version of GF12 and a qualitative focus group analysis of dual-panel members.

Results: Two hundred and fifty-one parents who have children attending *Tadikas* (pre-school) responded to the Malay GF12. In the reliability analysis, the internal consistency value was good; in the test-retest analysis, the intra-class correlation values were more than 0.7. In the exploratory factor analysis, two factors were extracted. In the confirmatory factor analysis, a single factor 12-item model did not fit well. Alternatively, a 2-factor-6-item model showed sufficient fit. The two constructs are comprised of Positive and Negative Items.

Conclusion: The Malay version of GF12 has adequate psychometric properties to measure family functioning in the Malay speaking population.

Keywords: *family functioning, Family Assessment Device, confirmatory factor analysis, reliability, construct validity, Malay*

Introduction

The vital role of the family in child growth and well-being is widely recognised[1]. Family and family life have long been recognised as complex historical, social, and cultural phenomena[2]. It is crucial to look at how the family uses their resources and how this forms part of their cultural pathway to health. A child's health status is also determined by the child and family history of health and illness and the parents' genetic dispositions[2]. Families play a significant role in the expression of various ailments, including psychiatric and oral disorders[3,4]. Parents' socioeconomic status and poor oral health habits have been linked directly to dental caries among children[4–6].

Nevertheless, the role of family functioning and its relationships in determining a child's oral health has not received much attention in the literature[7]. Family is the primary socialisation unit during childhood and is central in shaping engagement in health behaviour, including physical activity. Thus, it has been propounded that a child's health status could be directly linked to parents' health behaviour, including disease and genetic composition[2].

Family functioning may be described as a balance between family cohesion and adaptability to challenges within the family and the environment[7]. Health literacy of a family may influence health information's

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communication to the family, individual health beliefs and health-related behaviour[8]. A child is part of a more extensive family system and the family, in turn, is part of a broader neighbourhood or community system. Consequently, any changes in the family may affect the child and changes in child development[9].

Perceived family functioning can be studied extensively using a self-reported assessment tool, Family Assessment Device (FAD)[10]. The FAD is a 60-item measure built on the McMaster Model of Family Functioning[11,12]. A brief FAD version, the General Functioning subscale [GF12], has shown excellent psychometric properties in measuring general family functioning[13]. General Functioning subscale (GF12) is a shortened version of FAD with all the domains but reduced items for rating. The GF12 has been adapted into several languages for ease of application and usage within different ethnic communities worldwide[14–20].

Various methods have been employed to translate the instrument for cross-cultural adaptation and implementation concerning self-reported health outcome questionnaires[21–24]. The Dual Panel (DP) method utilised a consensus translation methodology with two panels[25]. The DP methodology appears to produce item wording that is perceived to be more acceptable[25].

An investigation of family functioning in the context of Malaysia's diverse family structures, from urban to the rural, single parent to extended families, within a multi-racial society can provide an understanding of the multi-factorial causes of chronic non-communicable oral diseases, including dental caries. There is a need to measure the impact of family functioning on the health of the Malaysian population. It is important to study how families function in these challenging times in the era of fast changing economic, social, and political landscapes. The GF12 instrument has been widely used in this pursuit, but translation and validation in the local language are requisites. Thus, the objective of this study was to conduct a cross-cultural adaptation and validation of the GF12 instrument of the McMaster Family Assessment Device (FAD) into the Malay language.

Methods

This study intended to adapt cross-cultural attributes to the GF12 instrument of the FAD and subsequent psychometric validation in the Malay language. The GF-12 instrument is self-administered with a 4-point Likert scale, ranging from 1 (strongly agree) to 4 (strongly disagree). The methodology adopted mechanism elaborated from guidelines and strategies by Guillemin and colleagues[26]. The Malay version was transcribed from the English version based on the semantic, operational and measurement equivalences. After translation to the Malay language, the questionnaire was pre-tested for its cognitive attribute, followed by pilot testing.

Translation of the English GF12 into the Malay Language

A dual-panel approach was utilised. This method was suggested by Hunt et al.[22] and supported by Swaine-Verdier et al.[23] for a concept based translation. Linguistic equivalence was not considered in this approach. The contemplation is based on the premise that obtaining a "natural" translation for an item in a new language is a difficult proposition. Hence, a word that is equivalent to the conceptual meaning is usually sought. Further, the translation is attempted to harness words that are in common usage.

The dual-panel translation procedure comprised the following main steps:

Panel 1: A panel of five bilingual healthcare professionals consisting of a nurse, a public health specialist, a community nutritionist, a dentist and a dental support assistant deliberated on the first draft of the Malay GF12 for conceptual equivalent with the English version.

Panel 2: This panel consisted of a monolingual nurse, a dental surgery assistant, and three persons from the targeted community (lay people) with Malay as their first language. This group focused on reviewing the first draft of the Malay GF12 to ensure the translations were expressed in a natural, everyday Malay language. Two members of the research team facilitated the thorough scrutiny of the translation process. At the end of the session, the panel agreed on the draft Malay GF12 with minor changes.

Validation of the draft Malay GF12

A mixed-methods approach with an exploratory sequential study design was employed. Face validity and content validity of the draft Malay GF12 was tested using a pre-test qualitative mechanism. At each stage, signed informed consent was obtained from the participating parent of the child. The consent form and study information sheet were sent to the parents through the school. Confidentiality and safe record-keeping were ensured to the participants at both data collection stages.

Pre-test: The pre-test of the draft Malay GF12 involved an expert panel of eight members (two general dentists, two dental public health specialists, two nurses, and two dental academicians) and a group of pre-school children's parents. The pre-test's purpose was to assess the presence of ambiguities in the translation process, identify items with inappropriate conceptual levels, and identify wordings that were confusing to understand[24]. The questionnaire was emailed to the eight-member expert panel who were bilingual. They were instructed to comment on the conceptual equivalence and wordings of the draft Malay GF12. The parents attended a focus group discussion (FGD) to assess whether the purpose, instructions and items were relevant and easily understood and whether the items measured were culturally relevant. The FGD was audio-recorded, and field notes were taken; interpretation biases and discrepancies in the observations were assessed using the 'member check' approach. The research team reviewed the two pre-test outcomes (expert panel and parents), and the Malay version of GF12 was finalised.

Pilot test: A total of 510 parents of 5-6-year-old children from 11 *Tadikas* (pre-school) randomly selected in the Petaling district were invited to participate in the pilot test. The parents answered the draft Malay GF12 and questions on pre-school children and parent's socio-demographic profiles (name, age, gender, marital status, religion, employment status, occupation, education, and ethnicity) in the presence of a member of the research team. The questionnaire was filled by either the mother or father. Studies have demonstrated similar parenting characteristics between mothers and fathers[27]. Participants were required to rate how well an item described their families. Subsequently, 15 parents were asked to answer the Malay GF12 questionnaire two weeks later.

Data analysis

Data from pre-test were analysed using NVivo-11 software. Textual data were obtained from the recorded data and field notes from the FGD using the verbatim transcription method. A detailed thematic

analysis followed the above procedure. IBM Statistical Package for the Social Science (Chicago, IL, USA) version 25 software was used for data analysis. The GF-12 instrument was self-administered among the respondents. The scores for negative items were reversed and the total score was calculated by summing up the scores of the 12 items. Descriptive statistics (frequency, mean and standard deviation) were used to describe parents' socio-demographic details. The psychometric properties of the Malay GF12 were assessed in terms of internal consistency, test-retest reliability, and construct validity. Cronbach's alpha coefficient measured the internal consistency of the Malay GF12. The homogeneity between the items was explored in this assessment. The statistical computations, including intra-class correlation (ICC) coefficient, exploratory factor analysis, confirmatory factor analysis (CFA) was employed to analyse test-retest reliability, construct validity, assessment of the measurement equivalence of Malay GF12, respectively. The analysis examined the instrument factors and factor loadings, including expressiveness of factor loadings with respect to the structure of GF12 through convergent and discriminant validity. IBM® SPSS® Amos™ software was utilised to perform the above computations. Amos™ uses the maximum likelihood estimation (MLE) method, which requires the assumption of multivariate normality (MVN). The expressiveness of factor loadings, residual variances and modification indexes were analysed. The best model fit with a value < 0.08 is represented as the Root Mean Square Error of Approximation (RMSEA). Good results for the Comparative Fit Index (CFI) and the Tucker-Lewis Index (TLI) are within the range of > 0.90. The Goodness-of-Fit statistic (GFI) calculates the proportion of variance accounted for by the estimated population covariance. The GFI cut-off point of ≥ 0.90 shows how closely the model comes to replicating the observed covariance matrix. The AGFI adjusts the GFI based upon degrees of freedom, and generally, the values of ≥ 0.90 indicate well-fitting models. Furthermore, Composite Reliability (CR) values > average variance extracted for the items (AVE) values indicate a good fit of the model. The AVE value is the average of squared factor loadings. For example, if all the factor loading are > 0.7, then the AVE will be > 50%. The higher the AVE, the better the model fit. To test for discriminant validity, the magnitude of the shared variance between the final two constructs (R^2) is checked to be less than the within construct variances (AVEs). A non-significant value for χ^2, values as close as possible to 1.00 for adjusted goodness-of-fit index (AGFI), values higher than 0.95 for normed fit index (NFI) and comparative fit index (CFI), a value as close as possible to zero for standardised root mean square residual (SRMR). A value lower than 0.05 for root mean square error of approximation (RMSEA) is indicative of a good fit between the estimated model and input data[28]. Hu et al. noted a value of RMSEA as high as 0.08 and values for CFI ranging from 0.90 to 0.95 for an acceptable fit of a confirmatory factor model[29]. In confirmatory factor analysis (CFA), the following cut-points were used to test for model fit: Chi-square/df < 3, CFI, TLI, GFI AGFI > 0.9 and RMSEA < 0.08[30].

The study was approved by the International Medical University (IMU) Joint Research and Ethics Committee (IMUR 157-2014). Consent was obtained from parents willing to participate in the study.

Results

In the pre-test of the draft Malay GF12, all the eight expert panel members and the eight parents who were approached responded. They found the translated

version of GF12 in the Malay language easy to adapt and simple. In item 1, the final Malay word for the word "*sukar*" (difficult) was changed to "*susah*" (a synonym of "*sukar*"), in item 2 the word "*krisis*" (crisis) was changed to "*masalah*" (a synonym of "*krisis*"), and in item 5 the word "*gusar*" (concern) was changed to "*risau*" (a synonym of "*gusar*"). Item 12 of the Malay version was rephrased from "*Kami bersikap terbuka di antara satu sama lain*" (We confide in each other) to "*Kami selesa berkongsi masalah antara satu sama lain*", which was conceptually equivalent. Table I shows the final Malay translation against the original version of the GF12 subscale after final amendments were made based on the review committee's decisions.

Table I: The Malay translation items and the corresponding GF12 items

No	English version	Malay version
1	Planning family activities is difficult because we misunderstand each other	*Merancang aktiviti keluarga menjadi susah kerana kami tidak sefahaman*
2	In times of crisis we can turn to each other for support	*Kami menyokong satu sama lain semasa ada kesukaran/ masalah*
3	We cannot talk to each other about the sadness we feel	*Kami tidak selesa berterus terang tentang kesedihan yang kami alami*
4	Individuals are accepted for what they are	*Setiap ahli keluarga diterima seadanya*
5	We avoid discussing our fears and concerns	*Kami mengelak dari membincangkan perasaan takut dan risau*
6	We can express feelings to each other	*Kami selesa meluahkan perasaan antara satu sama lain*
7	There are lots of bad feelings in our family	*Terdapat banyak perasaan kurang senang di dalam keluarga*
8	We feel accepted for what we are	*Kami rasa diterima seadanya*
9	Making decisions is a problem for our family	*Membuat keputusan adalah suatu kesukaran dalam keluarga kami*
10	We are able to make decisions about how to solve problems	*Kami boleh membuat keputusan bagaimana untuk menyelesaikan masalah*
11	We don't get along well together	*Kami tidak sehaluan antara satu sama lain*
12	We confide in each other	*Kami selesa berkongsi masalah antara satu sama lain*

For the pre-test, of the 510 parents who were approached, 251 parents agreed to participate (49.5% response rate). The parents' children were almost equally distributed in terms of gender (male = 50.2%, female = 49.8%) and age (5-year-olds = 46.2%, 6-year-olds = 53.8%). The majority of the parents were working full-time (46.6%) or were housewives (45.4%) and belonged to a low-income group (67.3%). Table II shows the participants' socio-demographic information. The parents were residing in urban and rural neighbourhoods. All the respondents were Malays (n=251), with the majority having education up to secondary school level (90%), and nearly half were working full-time (46.6%).

Table II: Socio-demographic characteristics of the children and their parents (n=251)

VARIABLE	n	%
Age of child/year		
5	116	46.2
6	135	53.8
Gender		
Male	126	50.2
Female	125	49.8
Ethnicity		
Malay	250	99.6
Indian	1	0.4
Parent's education level		
Primary school	7	2.8
Secondary school	202	80.5
Tertiary education *	24	9.5
No Education	18	7.2
Parent's employment status		
Full-time working	117	46.6
Self-employed	19	7.6
Housewife	114	45.4
Part-time	1	0.4

* Vocational training, college, and university.

The Cronbach alpha of the Malay GF12 was 0.89. In test-retest reliability analysis, the ICC values were more than 0.75. ICC values of 0.75 and 0.9 indicate good reliability[31].

In the final analysis, there were a total of 251 respondents. In exploratory factor analysis (EFA), the Keiser-Meir-Olkin (KMO) value was 0.8, which is considered good. Two factors were extracted: factor 1 consisting of positively worded items (2, 4, 6, 8, 10, 12) and factor 2 consisting of negatively worded items (1, 3, 5, 7, 9, 11) (Table III).

Table III: Results from Exploratory Factor Analysis (EFA) of the Malay General Functioning 12 items.

No	PATTERN MATRIX	FACTORS	
		1	2
12	We confide in each other	.920	
6	We can express feelings to each other	.913	
4	Individuals are accepted for what they are	.911	
8	We feel accepted for what we are	.835	
10	We are able to make decisions about how to solve problems	.777	
2	In times of crisis, we can turn to each other for support	.644	
5	We avoid discussing our fears and concerns		.784
9	Making decisions is a problem for our family		.778
3	We cannot talk to each other about the sadness we feel		.753
7	There are lots of bad feelings in the family		.743
1	Planning family activities is difficult because we misunderstand each other		.683
11	We don't get along well together		.676

The two factors explained 64% of the total variation in the 12 items. In confirmatory factor analysis (CFA), a single factor model (Figure I) did not fit well (Chi-square/df < 3, fit indices < 0.9 and RMSEA > 0.09).

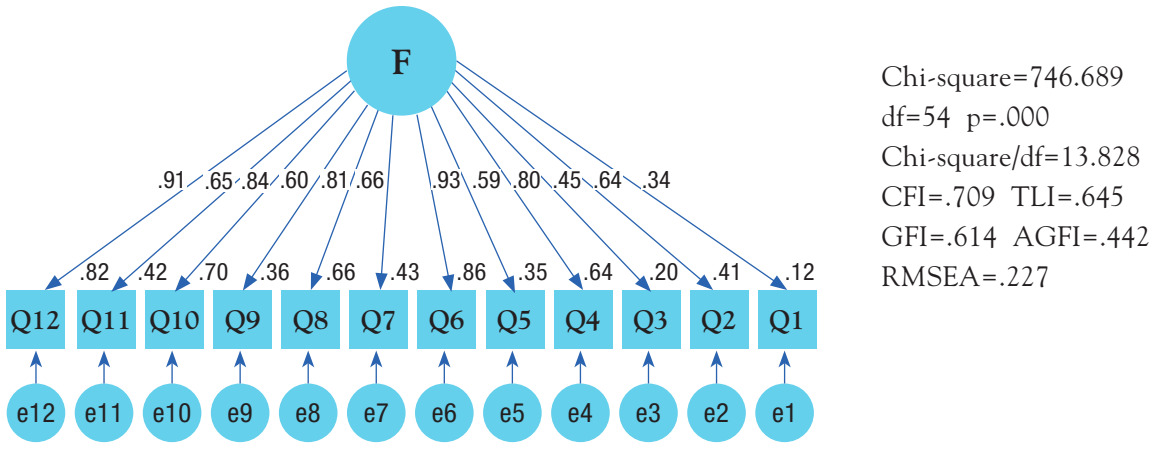

Figure I: Theoretical model

Based on the factor weights extracted, there were two distinct factors: items 1, 3, 5, 7, 9, and 11 in one factor and items 2, 4, 6, 8, 10 and 12 in the other. Hence, a two-factor model with the respective items was tested. The two-factor model (Figure II) did not fit well either (Chi-square/df < 3, fit indices < 0.9 and RMSEA > 0.09). Modification Indices (MI) showed high levels of associations for items 1, 2, 3, 4, 5 and 12 with other items. Hence, these items were dropped one at a time and the final model (Figure III & Table IV) with sufficient model fit (Chi-square/df < 3, fit indices > 0.9 and RMSEA < 0.09) was obtained. In the final model, the two-factor-three-item model was found to fit well. The RMSE value of 0.087 is very close to 0.08. Since the items in the model are meaningful, no further fine tuning was done. The first factor is a measure of Positive Items, and the second factor is a measure of Negative Items. Since no specific names could be given to the factors, we named them positive and negative factors. The AVE values were 0.736 and 0.732, respectively. The correlation value between the two factors was 0.67, which is less than the square roots of the AVE values. Hence there was sufficient discriminant validity between the two factors. The minimum factor loading was 0.77.

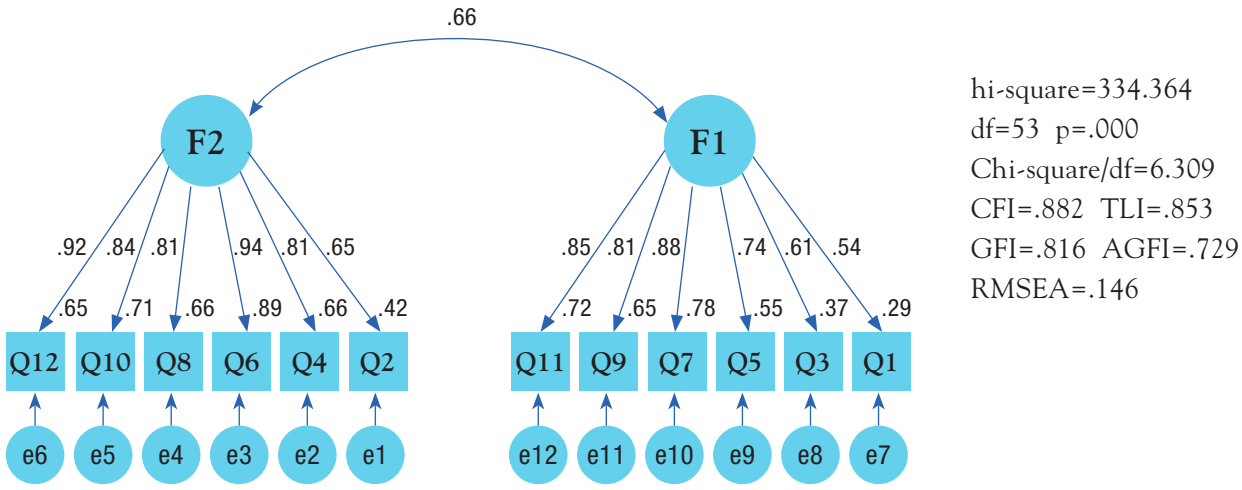

Figure II: Two-factor Model in confirmatory factor analysis (CFA)

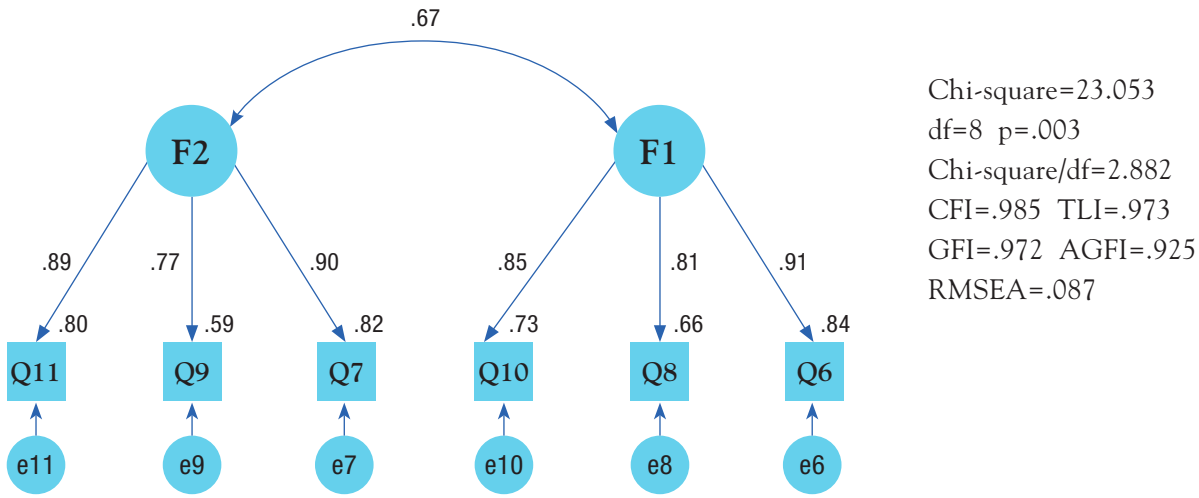

Figure III: After correcting, Final model

Table IV: Final model as per the description in the theoretical model (Figure III)

FACTOR	ITEMS	Factor Loading (FL)	Average Variance Extracted (AVE)	Composite Reliability (CR)
1	6. We can express feelings to each other	0.91	0.736	0.893
	8. We feel accepted for what we are	0.81		
	10. We are able to make decisions about how to solve problems	0.85		
2	7. There are lots of bad feelings in the family	0.90	0.732	0.891
	9. Making decisions is a problem for our family	0.77		
	11. We don't get along well together	0.89		

Discussion

This study aimed to explore a cross-cultural adaptation and validation of the Malay GF12 of the FAD. The study findings indicate that the Malay GF12 consisting of 2 factors with three items in each factor is valid and reliable to assess family functioning in the Malaysian setting. The reliability of the Malay GF12 was tested in terms of internal consistency and test-retest reliability, whereby findings were in agreement with the Portuguese and French FAD-GF12 studies[32,33]. The Cronbach alpha of the Malay GF12 was 0.89, which indicates a high level of internal consistency supporting the previous findings of Spanish and Dutch versions[34,35]. For test-retest reliability analysis, the ICC value was more than 0.75, which is considered good and in agreement with the ICC value for the French FAD-GF12[33,36]. Georgiadis et al. found internal consistency 0.89, and Zubrick et al. alpha 0.88, comparable to our study 0.89[37,38]. However, studies have reported that the instrument may show a different behaviour between families of different cultures and socioeconomic backgrounds, limiting study findings' generalisability to other cultures[39].

In the confirmatory factor analysis, the original 12-item model did not produce a well-fitted model because the RMSEA value of 0.227 was larger than the recommended value of less than 0.05 for a well-fitted model[40]. Instead, a two-factor and six-item model showed a sufficient fit. The results indicate the feasibility of administering six of the twelve items of the Malay GF12 (3 positively worded and 3 negatively worded items) to measure family functioning in the Malaysian population. Our study findings are different from the Italian GF-12 subscale validation findings, which has a 4-factor model with the following domains: competence, emotional, communication, and centre-on-self [41]. A possible explanation could be attributed to the differences in education levels and cultures between the two populations, which conceptualise normal family functioning differently[42]. Different cultural norms regarding family functioning may have affected the results, varying according to socioeconomic status. In the final analysis of the study, items 1, 2, 3, 4, 5 and 12 will be maintained, despite the correlation. Operationally, this option would allow for decision-making in the analysis phase.

Finally, the process of translating and cross-cultural adaption is classified in a hierarchy, from requiring minimum effort (Category 1—Forward-only translation) to substantial effort (Category 6—Back translation, monolingual, and bilingual tests)[43]. Considering this study's methods of translation and cultural adaption, it is classified in Category 4.

Limitations

Malaysia is a multi-racial country consisting of Malays, Chinese, Indians and indigenous peoples. As almost 100% of the respondents in this study were Malays, it is not a true representation of the population at large. The instrument may show different behaviour in other Malaysian races or cultural contexts. It may not be appropriate to use this Malay GF12 in its current form for participants of the other ethnicities within Malaysia until further validations have been carried out. Further studies are recommended to assess the validity of the Malay GF12 across different cultural settings and establish the cut-off point between "pathological" and "healthy" family functioning in the Malaysian population.

Conclusion

The results of our study show that the Malay GF12 is a valuable tool for assessing family functioning. This study's findings indicate that 6 (3 positively worded and 3 negatively worded items) of the 12 items of the Malay GF12 have adequate psychometric properties to measure family functioning in the Malaysian context. As family functioning is embedded in the cultural context, further studies should compare groups across different cultural settings to increase the index's specificity.

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Case Report

Postural improvement in young deaf and mute boy in post 2 weeks pineal gland tumour removal after 3 balance rehabilitation: A Case Study

Zuraida Zainun, Zamzuri Idris, Muhammad Munzir Zuber Ahmad, Nur Syakirah Bt Che Mat Amin

Pineal region tumours are primary central nervous system (CNS) tumours. Pineal region tumours may cause increased pressure inside the skull due to the production of too much CSF or blockage of its normal flow known as hydrocephalus. Imbalance is one of the features in this case. Vestibular Rehabilitation (VRT) is a specific form of physical therapy designed to habituate symptoms and promote adaptation to and substitution for various aspects of deficits related to a wide variety of balance disorders. Bal Ex is a home-based module of VRT with specific modules that are available in three forms; manual book, poster and DVD. This module was developed with a combination of customized Cawthorned Cookseey Exercise and prayer movements. The patient is a 14-year-old boy, disabled (mute and deaf), known case of pineal gland tumour since 2016, then post tumour removal 2 weeks ago. The patient experienced balance problem 8 years ago before he was diagnosed with pineal tumour. He did not complain of any dizziness and vertigo according to his mother. The patient then underwent intensive BAL Ex therapy inward for 3 sessions starting with Level 1, once per day, 40 minutes each session, and without taking any medicine during the treatment. He underwent one-to-one sessions with the trainer and also followed the balance exercise video in every session. After 1 week of balance exercise only in level 1, the patient showed a small difference and 10% improvement.

Keywords: *Bal Ex, Postural improvement, Bal Ex Module, imbalance*

INTRODUCTION

Pineal gland tumour is not a common type of tumour which is reported at less than 1% of the primary type of brain tumour[1]. This type of tumour is divided into four different grades referred to their characteristics and it originates from a normal cell inside the pineal gland that is commonly experienced among children compared to adults. The exact location of the pineal gland is in the third ventricle center part of the brain and the primary central nervous system that is responsible for melatonin hormone secretion[2].

Overproduction of the CSF or obstruction of the drainage can cause hydrocephalus in pineal gland tumors. So symptoms are most often caused by blockage of the cerebrospinal fluid flow which then causes obstructive hydrocephalus. Common symptoms faced by the patient include headache, nausea, vomiting, imbalance and double vision[3].

The formal treatment for these tumours is surgery removal proceeded with the biopsy of the tumour tissues to determine the grade and staging of the tumour. After the surgery, there are a few cases that need to be continued with radiation and chemotherapy.

Case Report

A 14-year-old disabled, mute and deaf boy, a known case of pineal gland tumour since 2016, then post tumour removal 2 weeks ago from the clerking date, presented with a balance problem 8 years ago. He was diagnosed with profound hearing loss and was underwent unilateral cochlear implant (CI) surgery. There was no detailed

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assessment done and referral for this problem. Post-CI, his parents reported poor speech and communication even after they followed all the speech therapy sessions. Till now there is no speech seen and not much progress reported by his mother. Detailed pictures of pre- and post-tumour removal are shown in Figure I. He did not complain of any dizziness and vertigo apart from imbalance and difficulty in walking after surgery.

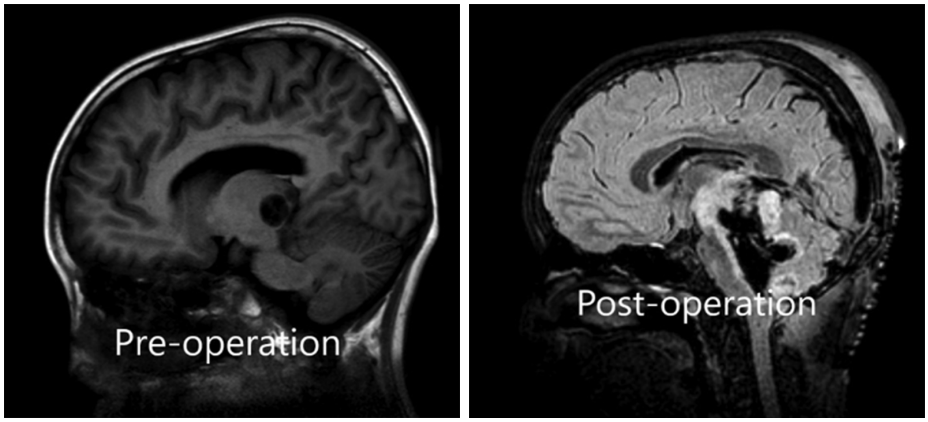

Figure I: MRI finding in pre- and post-pineal tumour removal

The patient then underwent 3 sessions of intensive BAL EX therapy in-ward starting with Level 1, once per day, 40 minutes each session, and without taking any medicine during the treatment. To evaluate the postural control pre- and post-therapy we used the Bal Exzz Foam test pre- and post-balance rehabilitation. This Bal Exzz Foam test has a structured scoring foam that is divided into seven sections (Table I). A positive Fukuda test has been identified (Table I). The patient previously experienced symptoms in the past 8 years before he was diagnosed with pineal tumour but improved after the treatment.

Table I: Bal Ex Scoring Foam

LEVEL	DESCRIPTION	PRE THERAPY	POST 3 SESSIONS THERAPY
1	Stand on the floor with arms across your chest and feet together and hold for 30 seconds (opened eyes)	Normal	Normal
2	Stand on the floor with arms across your chest and feet together and hold together and hold for 30 seconds (closed eyes)	< 4 seconds	< 5 seconds
3	Stand on the floor with arms across your chest, toe touching the other side of heel and hold for 30 seconds (opened eyes)	< 2 seconds	< 2 seconds
4	Stand on the floor with arms across your chest, toe touching the other side of heel and hold for 30 seconds (closed eyes)	< 1 second	< 2 seconds
5	Stand on a 3-inch-high density foam cushion with your arms crossed, feet together and hold for 30 seconds (opened eyes)	< 3 seconds	< 3 seconds
6	Stand on a 3-inch-high density foam cushion with your arms crossed, feet together and hold for 30 seconds (closed eyes)	< 2 seconds	< 3 seconds
7	Fukuda test	Unable to perform	Unable to perform

VRT is a type of physical therapy that aims to habituate symptoms and encourage adaptation to and substitution for various aspects of deficits associated with a wide variety of balance problems. The vestibular system must be stimulated and retrained, hence the majority of VRT activities include head movement. The prognosis for patients with post-removal pineal gland tumour is good[3].

Bal Ex is a home-based module that is available in three forms namely video. manual book, poster, and DVD. The Bal Ex Home-based balance is a VRT with specific modules and a video guide. To assist people with various balance disorders, it includes nine distinct languages (Malay, English, Mandarin, Tamil, Hokkien, Nigeria, Parsian, and Arabic)[4]. The Bal-Ex module video is a completely structured home-based video and audio-guided tool designed to help individuals with Peripheral Vestibular Disorder (PVD). This module was created using a modified exercise and prayer movements. One of the VRT exercises is foam exercise. There are numerous advantages to use this physical exercise module. This exercise consists of 20 movements and is divided into 3 levels targeting specific functions of balance organs (Table II). Bal Ex is an adaptation from Customized Cawthorned Cookseey Exercise and prayer movement.

Figure II: Balance rehabilitation using Bal Ex video session

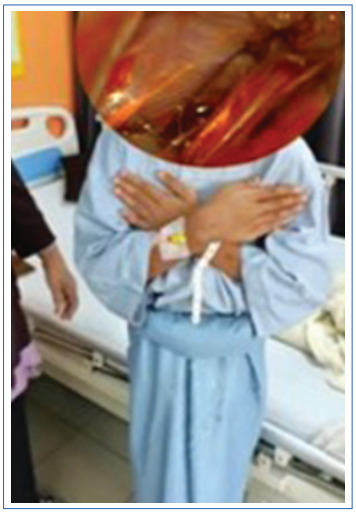

Table II: Three levels in the Bal Ex module video

Level 1	Level 2	Level 3
• Head & neck	• Positioning	• Postural
• Eye focusing	• Daily activities (i.e., prayer, up and down)	• Increase the postural control
• Heaviness of the neck	• Return to normal daily activities	• Return to normal walk, running and use a stair

Discussion and Conclusion

Pineal region tumour is one of the commonest central lesions or tumours in the young age population. Any central lesion in the brain can cause a balance disorder that can impair quality of life. Poor postural control, recurrent fall, floating sensation are common balance symptoms. Usually, the prognosis for patients with post-removal pineal gland tumour is good. In this case, the pre- and post-op patient experienced poor postural control and was unable to walk properly. After several sessions of intervention using the Bal Ex module in a balance rehabilitation clinic in level 1, the patient showed some recovery whereby he improved with mild imbalance after 3 sessions and more for the head and neck movement. Since the patient is mute, we were unable to have proper feedback and family member feedback was used for this patient. Bal Ex is a home-based module that can be used and practiced at home. In this case, it was able to improve the postural control when the patient continuously underwent balance rehabilitation at home with family member support. In every tumour case, one of the key supports post-operation that needs to be emphasized is balance rehabilitation. If the patient's postural control is not improved, it will cause poor quality of life whereby the patient cannot walk and continue daily activities normally. Surgical and physiotherapy is a great combination of therapy in tumour cases having balance problems.

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